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(54) Title: AMINE DERIVATIVES

(57) Abstract: An amine derivative, its tautomeric or stereoisomeric form, or a salt thereof which has vanilloid receptor 1 (VR1) antagonistic activity, is disclosed. The amine derivative has an excellent activity as VR1 antagonist and useful for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and/or inflammatory disorders.

WO 03/014064 A1

AMINE DERIVATIVES

TECHNICAL FIELD

The present invention relates to an amine derivative, which is useful as an active ingredient of pharmaceutical preparations. The amine derivatives of the present invention have vanilloid receptor 1 (VR1) antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and/or inflammatory disorders.

BACKGROUND ART

Vanilloid compounds are characterized by the presence of vanillyl group or a functionally equivalent group. Examples of several vanilloid compounds or vanilloid receptor modulators are vanillin (4-hydroxy-3-methoxy-benzaldehyde), guaiacol (2-methoxy-phenol), zingerone (4-/4-hydroxy-3-methoxyphenyl/-2-butanon), eugenol (2-methoxy4-/2-propenyl/phenol), and capsaicin (8-methy-N-vanillyl-6-nonene-amide).

Among others, capsaicin, the main pungent ingredient in "hot" chili peppers, is a specific neurotoxin that desensitizes C-fiber afferent neurons. Capsaicin and its analogues, such as resiniferatoxin, are shown to be effective in the treatment of urological disorder e.g., urinary incontinence and overactive bladder, due to the desensitization of C-fiber afferent neurons [(Michael B Chancellor and William C. de Groat, The Journal of Urology Vol. 162, 3-11, 1999) and (K.E. Andersson et al., BJU International, 84, 923-947, 1999)]. However, the mechanism in which capsaicin

and other analogues cause the desensitization of C-fiber afferent neurons is very complicated.

Vanilloid receptor (VR) is a specific neuronal membrane recognition site for capsaicin. It is expressed almost exclusively by primary sensory neurons involved in nociception and neurogenic inflammation. The VR functions as a cation-selective ion channel with a preference for calcium. Capsaicin interacts with VR1, which is a functional subtype of the VR and predominantly expressed in cell bodies of dorsal root ganglia (DRG) or nerve endings of afferent sensory fibers including C-fiber nerve endings [Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D: The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 21: 531-543, 1998]. The VR1 was recently cloned [Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D: Nature 389: 816-824, (1997)] and identified as a nonselective cation channel with six transmembrane domains that is structurally related to the TRP (transient receptor potential) channel family. Binding of capsaicin to VR1 allows sodium, calcium and possibly potassium ions to flow down their concentration gradients, causing initial depolarization and release of neurotransmitters from the nerve terminals.

VR1 can therefore be viewed as a molecular integrator of chemical and physical stimuli that elicit neuronal signals in a pathological conditions or diseases.

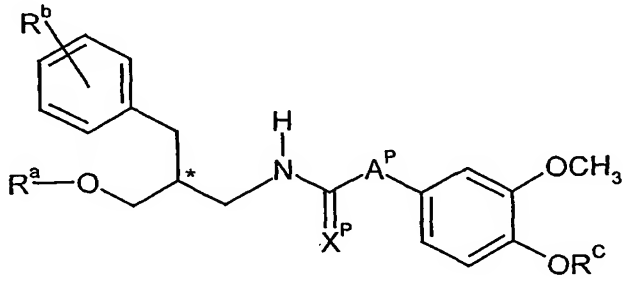
There are abundant of direct or indirect evidence that shows the relation between VR1 activity and diseases such as pain, ischaemia, and inflammatory (e.g., WO 99/00115 and WO00/50387). Further, it has been demonstrated that VR1 transduce reflex signals that are involved in the overactive bladder of patients who have damaged or abnormal spinal reflex pathways [De Groat WC: A neurologic basis for the overactive bladder. Urology 50 (6A Suppl): 36-52, 1997]. Desensitisation of the afferent nerves by depleting neurotransmitters using VR1 agonists such as capsaicin has been shown to give promising results in the treatment of bladder dysfunction

associated with spinal cord injury and multiple sclerosis [(Maggi CA: Therapeutic potential of capsaicin-like molecules - Studies in animals and humans. Life Sciences 51: 1777-1781, 1992) and (DeRidder D; Chandiramani V; Dasgupta P; VanPoppel H; Baert L; Fowler CJ: Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: A dual center study with long-term follow-up. J. Urol. 158: 2087-2092, 1997)].

It is anticipated that antagonism of the VR1 would lead to the blockage of neurotransmitter release, resulting in prophylaxis and treatment of the condition and diseases associated with VR1 activity.

It is therefore expected that antagonists of the VR1 can be used for prophylaxis and treatment of the condition and diseases including urology disorder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders. "Urological disorder" used herein refers to e.g., urinary incontinence and overactive bladder. Urinary incontinence and overactive bladder encompass detrusor hyper-reflexia, detrusor instability and urgency/-frequency syndrome, such as urge urinary incontinence and the like.

WO 00/50387 discloses the compounds having a vanilloid receptor agonist activity represented by the general formula:



wherein;

X^P is an oxygen or sulfur atom;

A^P is $-NHCH_2-$ or $-CH_2-$;

R^a is a substituted or unsubstituted C_{1-4} alkyl group, or $R^{a1}CO-$;

wherein

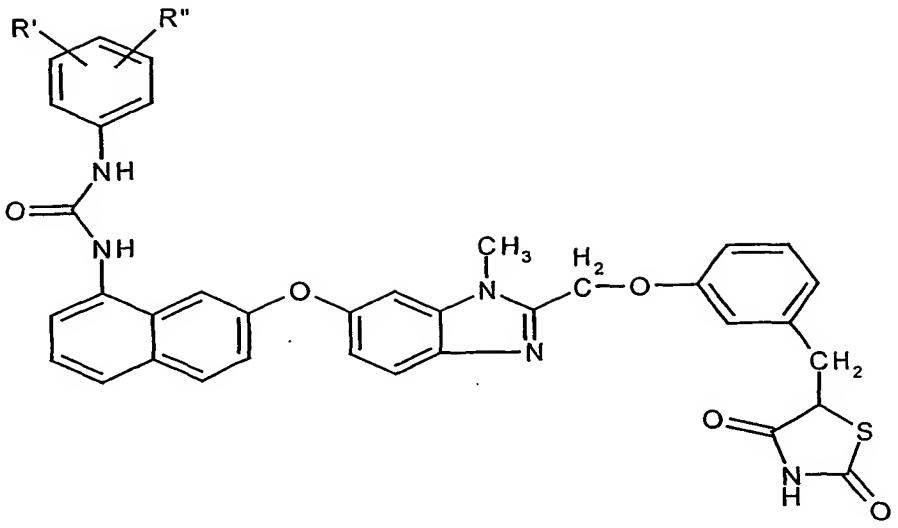
R^{a1} is an alkyl group having 1 to 18 carbon atoms, an alkenyl group having 2 to 18 carbon atoms, or substituted or unsubstituted aryl group having 6 to 10 carbon atoms;

R^b is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkoxy group having 1 to 6 carbon atoms, a haloalkyl group having 1 to 6 carbon atoms or a halogen atom;

R^C is a hydrogen atom, an alkyl group having 1 to 4 carbon atom, an aminoalkyl, a diacid monoester or α-alkyl acid; and

the asteric mark * indicates a chiral carbon atom, and their pharmaceutically acceptable salts.

WO 00/61581 discloses amine derivatives represented by the general formula:

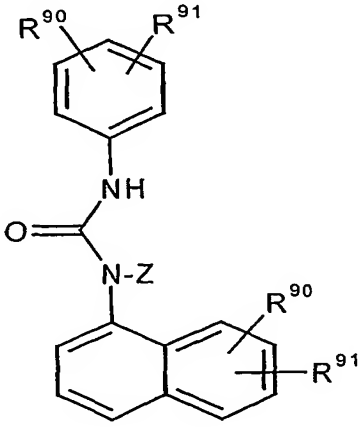


wherein

(R', R") represent (F, F), (CF_3, H), or (iPr, iPr)

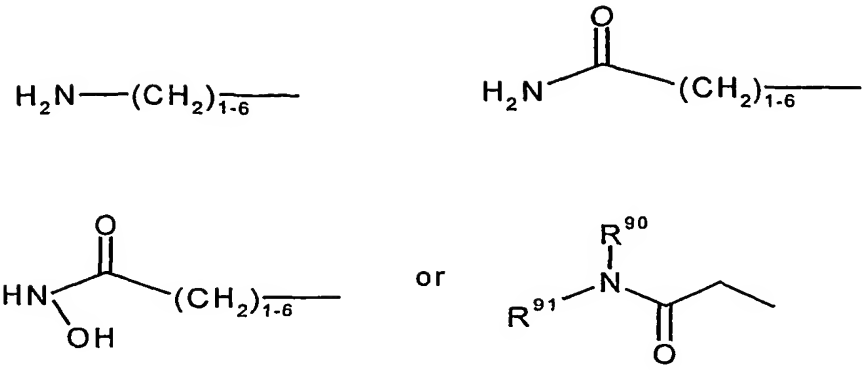
as useful agents for diabetes, hyperlipemia, arteriosclerosis and cancer.

WO 00/75106 discloses the compounds represented by the general formula:



wherein

Z represents



in which

R^{90} is hydrogen, C_{1-12} alkyl, C_{3-8} cycloalkyl, or the like, and R^{91} is amino-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, or hydroxyamino-carbonyl C_{1-6} alkyl; and

R^{90} and R^{91} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkoxy, fluoro, chloro, bromo, iodo, and nitro;

as useful agents for treating MMP-mediated diseases in mammals.

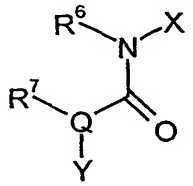
However, none of these reference discloses simple phenyl-naphthyl urea derivatives having VR1 antagonistic activity.

The development of a compound, which has effective VR1 antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urology disorder including urinary incontinence and/or overactive bladder, has been desired.

SUMMARY OF THE INVENTION

As the result of extensive studies on chemical modification of amine derivatives, the present inventors have found that the compound of novel chemical structure related

to the present invention have unexpectedly excellent VR1 antagonistic activity. This invention is to provide the following general formula (I), its tautomeric or stereoisomeric form, and the salts thereof:



(I)

wherein

X represents C_{3-8} cycloalkyl optionally fused by benzene, thienyl, thienyl C_{1-6} straight alkyl, quinolyl, 1,2-oxazolyl substituted by R^1, naphthyl optionally substituted by R^4 and R^5, phenyl fused by C_{4-8} cycloalkyl, phenyl fused by saturated C_{4-8} heterocycle having one or two O atoms, carbazolyl of which N-H is substituted by N-R^1, phenyl fused by indanone, phenyl fused by indan, phenyl fused by cyclohexanone, phenyl fused by dihydrofuranone, phenyl substituted by R^1, R^2 and R^3, phenyl C_{1-6} straight alkyl of which phenyl is substituted by R^1, R^2 and R^3, phenyl fused by unsaturated 5-6 membered hetero ring having one or two hetero atoms selected from the group consisting of N, O, S, and SO_2, wherein the hetero ring is optionally substituted by R^1,

wherein

R^1, R^2 and R^3 are identical or different and represent hydrogen, halogen, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkylcarbamoyl, carbamoyl, straight-chain or branched C_{1-6} alkoxy, carboxyl, nitro, amino, straight-chain or branched C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, morpholino, straight-chain or branched C_{1-6} alkoxycarbonyl, benzyl, phenoxy, halogen substituted phenoxy,

straight-chain or branched C_{1-6} alkylthio, straight-chain or branched C_{1-6} alkanoyl, straight-chain or branched C_{1-6} alkanoylamino, hydroxy substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkoxy, C_{1-6} alkyl substituted 4,5-dihydro-1,3-oxazolyl, 1,2,3-thiadiazolyl, the substituent represented by the formula $-SO_2-NH-R^{12}$ (R^{12} represents hydrogen, 5-methyl-isoxazole, or 2,4-dimethylpyrimidine) or

phenyl optionally substituted by one to three substituents,

wherein

the substituents are each identical or different and selected from the group consisting of hydrogen, halogen, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkanoyl, and carboxy;

R^4 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

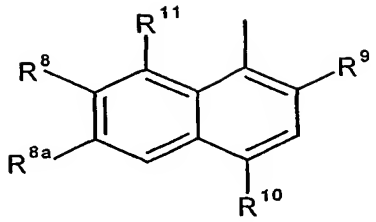
R^5 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

Q represents CH or N;

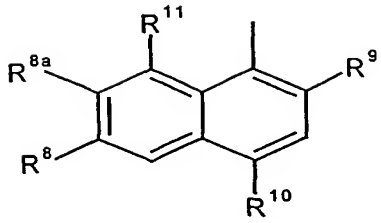
R^6 represents hydrogen or methyl;

R^7 represents hydrogen or methyl; and

Y represents

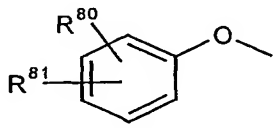


or



wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} cycloalkyl-methoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, C_{1-6} alkylsulfonamino, or the group represented by the formula



wherein

R^{80} and R^{81} are each identical or different and represent hydrogen, halogen, or straight-chain or branched C_{1-6} alkoxy;

R^{8a} represents hydrogen or halogen;

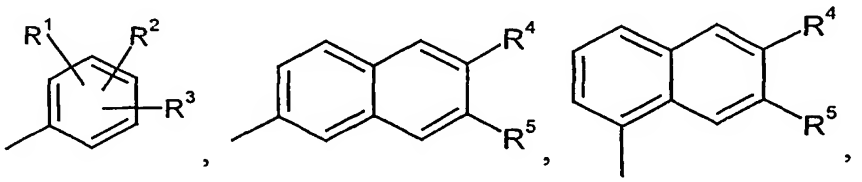
R^9 and R^{11} are each identical or different and represent hydrogen, halogen, or nitro; and

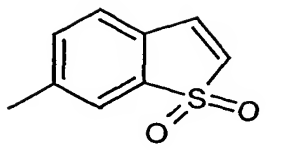
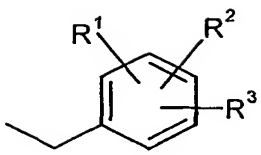
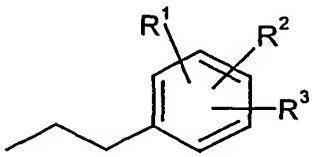
R^{10} represents hydrogen, halogen, carboxy, carbamoyl, cyano, or straight-chain or branched C_{1-6} alkyl optionally substituted by the substituent, which substituent is selected from the group consisting of hydroxy, amino, di(straight-chain or branched C_{1-6} alkyl)amino, piperidino, morpholino, and methyl-piperazino.

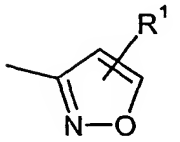
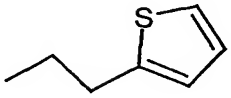
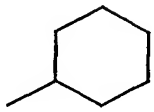
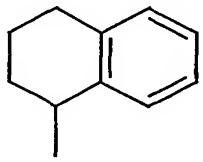
The compounds of the present invention suprisingly show excellent VR1 antagonistic activity. They are, therefore, suitable especially as VR1 antagonists and in particular for the production of medicament or medical composition, which may be useful to treat urological disorder. Since the amine derivatives of the present invention antagonize VR1 activity, they are useful for treatment and prophylaxis of diseases as follows: urology disorder (e.g., urinary incontinence and overactive bladder), chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and/or inflammatory disorders.

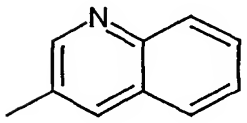
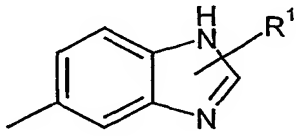
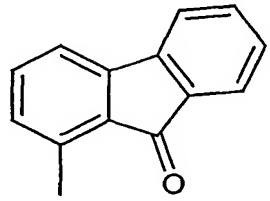
In another embodiment, the amine derivative of the formula (I) is those wherein;

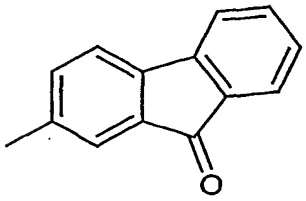
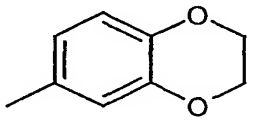
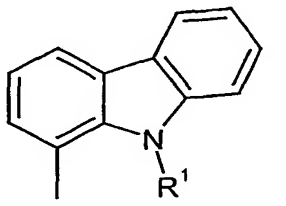
X represents

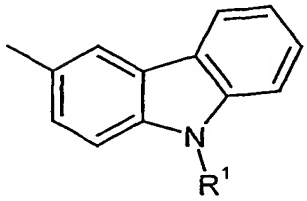
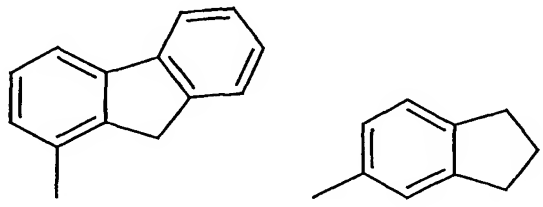


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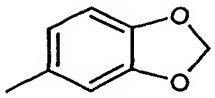


wherein

R^1, R^2 and R^3 are different or identical and represent hydrogen, halogen, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkylcarbamoyl, carbamoyl, straight-chain or branched C_{1-6} alkoxy, carboxyl, nitro, amino, straight-chain or branched C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, morpholino, straight-chain or branched C_{1-6} alkoxycarbonyl, benzyl, phenoxy, halogen substituted phenoxy, straight-chain or branched C_{1-6} alkylthio, straight-chain or branched C_{1-6} alkanoyl, straight-chain or branched C_{1-6} alkanoylamino, hydroxy substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkoxy, C_{1-6} alkyl substituted 4,5-dihydro-1,3-oxazolyl, 1,2,3-thiadiazolyl, the substituent represented by the formula $-SO_2-NH-R^{12}$ (R^{12} represents hydrogen, 5-methyl-isoxazole, or 2,4-dimethylpyrimidine) or

phenyl optionally substituted by one to three substituents,

wherein

the substituents are each different or identical and selected from the group consisting of hydrogen, halogen, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkanoyl, and carboxy;

R^4 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

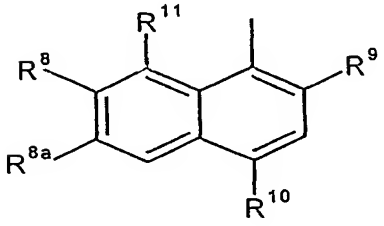
R^5 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

Q represents CH or N;

R^6 represents hydrogen or methyl;

R^7 represents hydrogen or methyl; and

Y represents



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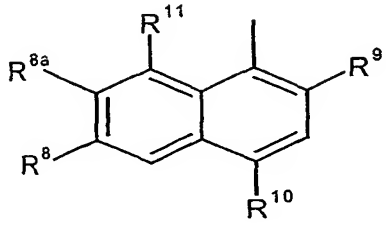
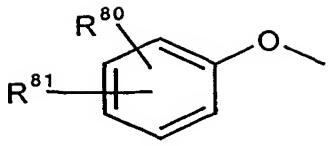


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} C_{3-6} cycloalkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, straight-chain or branched C_{1-6} alkylsulfonamino, or the group represented by the formula



wherein

R^{80} and R^{81} are each identical or different and represent hydrogen, halogen, or straight-chain or branched C_{1-6} alkoxy;

R^{8a} represents hydrogen or halogen;

R^{9} represents hydrogen or halogen;

R^{10} represents hydrogen, halogen, or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen, halogen, or nitro

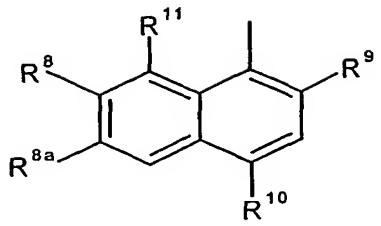
or a salt thereof.

In yet another embodiment, the amine derivative of the formula (I) is those wherein;

R^{6} represents hydrogen;

R^{7} represents hydrogen;

Y represents



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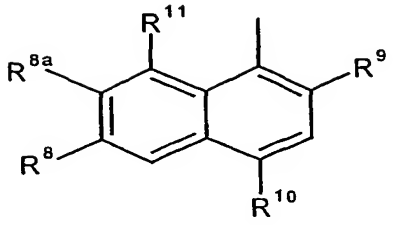


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} C_{3-6} cycloalkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, or C_{1-6} alkylsulfonamino;

R^{8a} represents hydrogen, chloro, or fluoro;

R^9 represents hydrogen or halogen;

R^{10} represents hydrogen, halogen or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen or halogen;

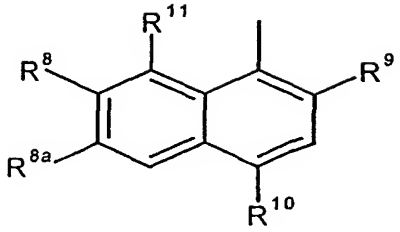
or a salt thereof.

In yet another embodiment, the amine derivative of the formula (I) is those wherein;

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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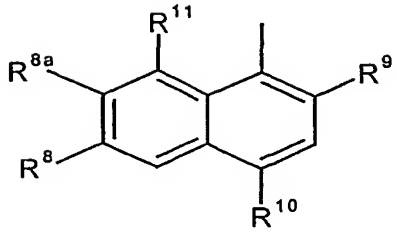


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} C_{3-6} cycloalkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, or straight-chain or branched C_{1-6} alkyl-sulfonamino;

R^{8a} represents hydrogen;

R^9 represents hydrogen, bromo, chloro, or fluoro;

R^{10} represents hydrogen,halogen or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen, chloro, or fluoro

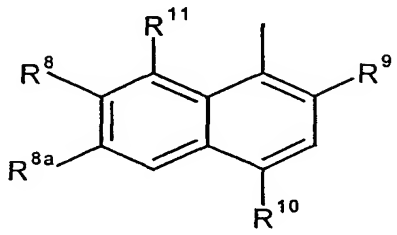
or a salt thereof.

In yet another embodiment, the amine derivative of the formula (I) is those wherein;

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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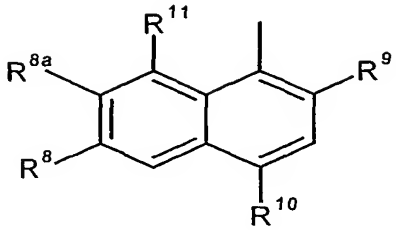


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} cyclo-alkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, or straight-chain or branched C_{1-6} alkylamino;

R^{8a} represents hydrogen;

R^9 represents bromo or chloro;

R^{10} represents bromo, chloro, or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen

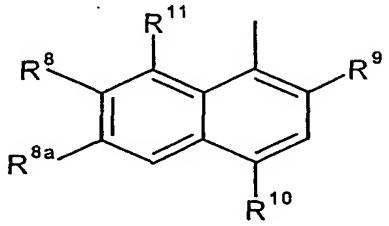
or a salt thereof.

In yet another embodiment, the amine derivative of the formula (I) is those wherein;

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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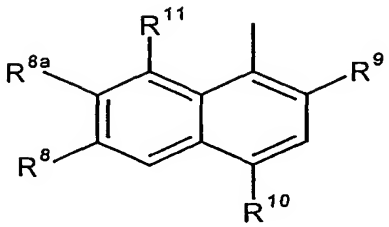


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} cycloalkyl-methoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, or straight-chain or branched C_{1-6} alkyl-amino;

R^{8a} represents hydrogen;

R^9 represents chloro;

R^{10} represents chloro; and

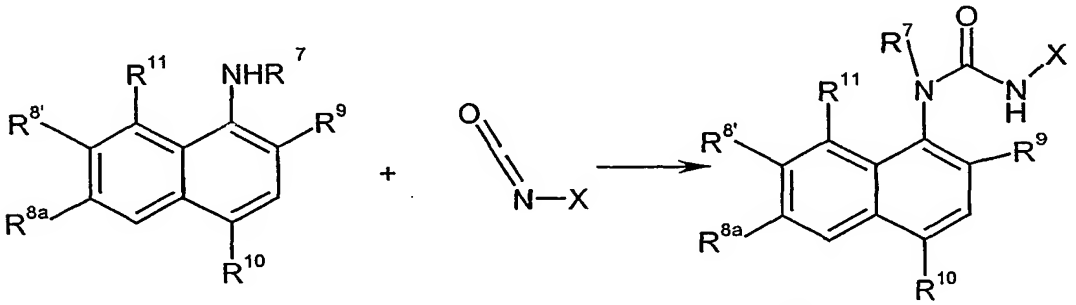
R^{11} represents hydrogen

or a salt thereof.

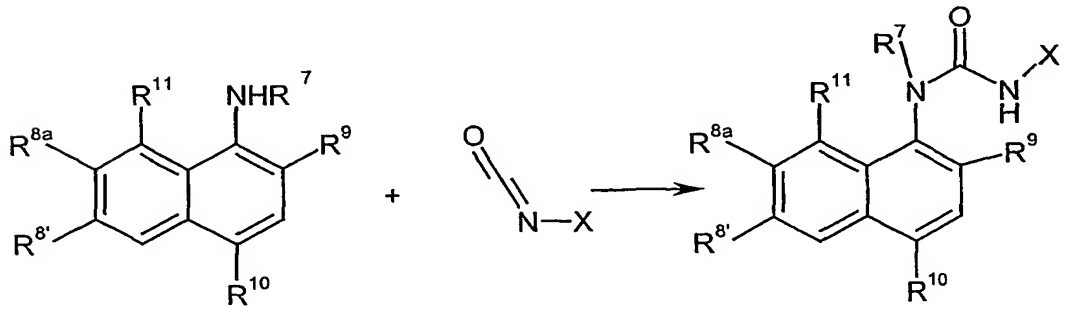
The present invention further provides the medicament having one of the compounds mentioned-above and one or more pharmaceutically acceptable excipients.

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by the general methods [A]-[K] below. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3rd Edition, John Wiley, New York, 1999)" by Greene and Wuts.

[Method A]



[I-a]



[I-a']

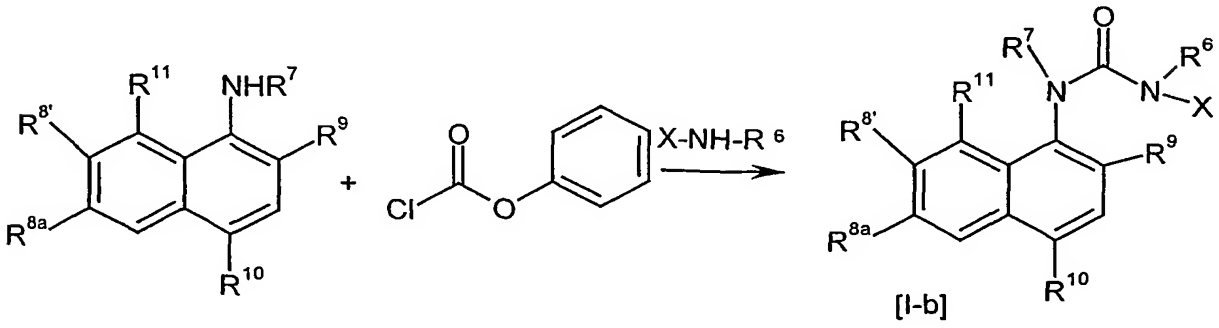
The compound [I-a] and the compound [I-a'], wherein $R^{8'}$ is hydroxy, strait-chain or branched C_{1-6} alkoxy, strait-chain or branched C_{1-6} alkoxy, benzoyloxy, straight-chain or branched strait-chain or branched C_{1-6} alkenyloxy, C_{3-8} cycloalkylmethoxy,

phenyl C_{1-6} alkylamino, straight-chain or branched C_{1-6} alkylamino, or di(straight-chain or branched C_{1-6} alkyl)amino and R^7, R^9, R^{10}, R^{11}, and X are the same as defined above, can be prepared by the reaction of a substituted naphthylamine and isocyanate. The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N,N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

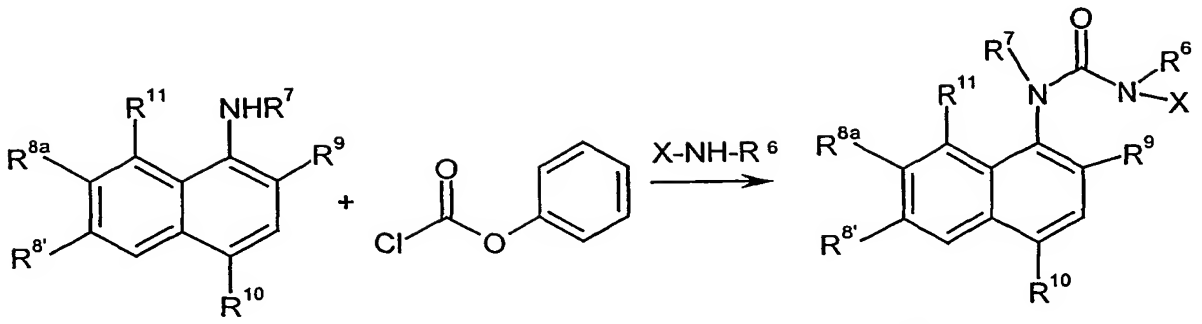
The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The substituted naphthylamine and isocyanate are commercially available or can be prepared by the use of known techniques.

[Method B]



[I-b]



[I-b']

The compound [I-b] and the compound [I-b'], wherein R^6, R^7, R^{8a}, $R^{8'}$, R^9, R^{10}, R^{11}, and X are the same as defined above, can be prepared by (1) reacting a substituted naphthylamine and phenylchloroformate, and (2) adding amine represented by the formula X-NH-R^6 (wherein R^6 and X are the same as defined above) to the reaction mixture. The reaction (1) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50°C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The reaction can be advantageously carried out in the presence of a base including, for instance, an alkali metal hydride such as sodium hydride and potassium hydride; alkali metal carbonates such as sodium carbonate and potassium carbonate; alkali metal hydrogen carbonates such as sodium hydrogen carbonate and potassium

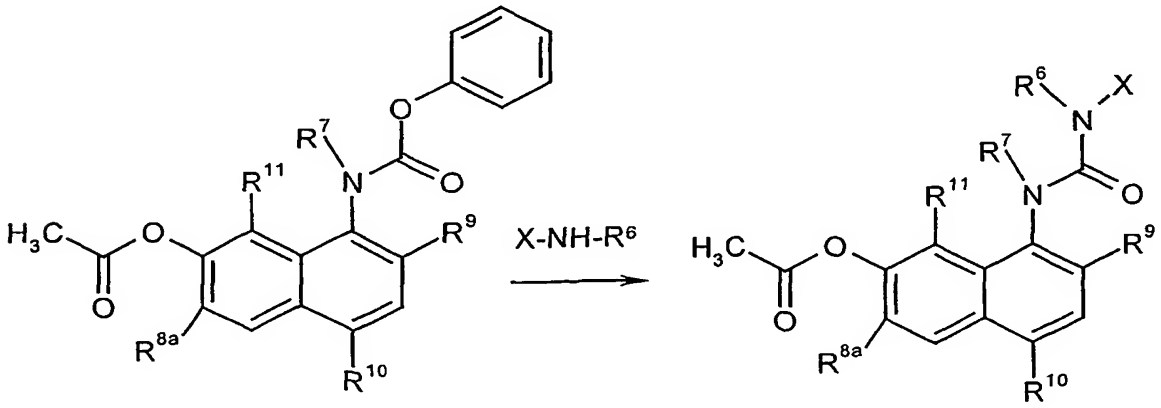
hydrogen carbonate; organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, and others.

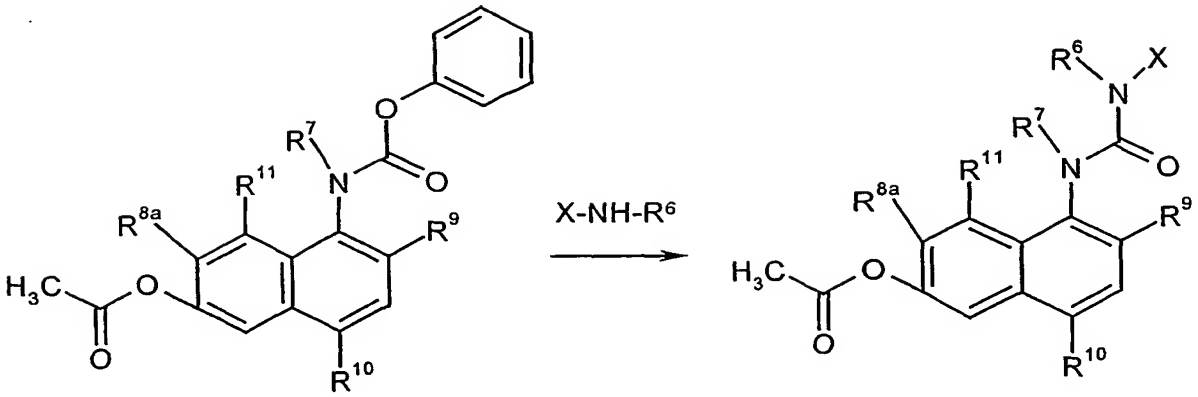
The reaction (2) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N,N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 1 hour to 48 hours and preferably 2 to 24 hours.

The substituted naphthylamine, phenylchloroformate and amine are commercially available or can be prepared by the use of known techniques.

[Method C]





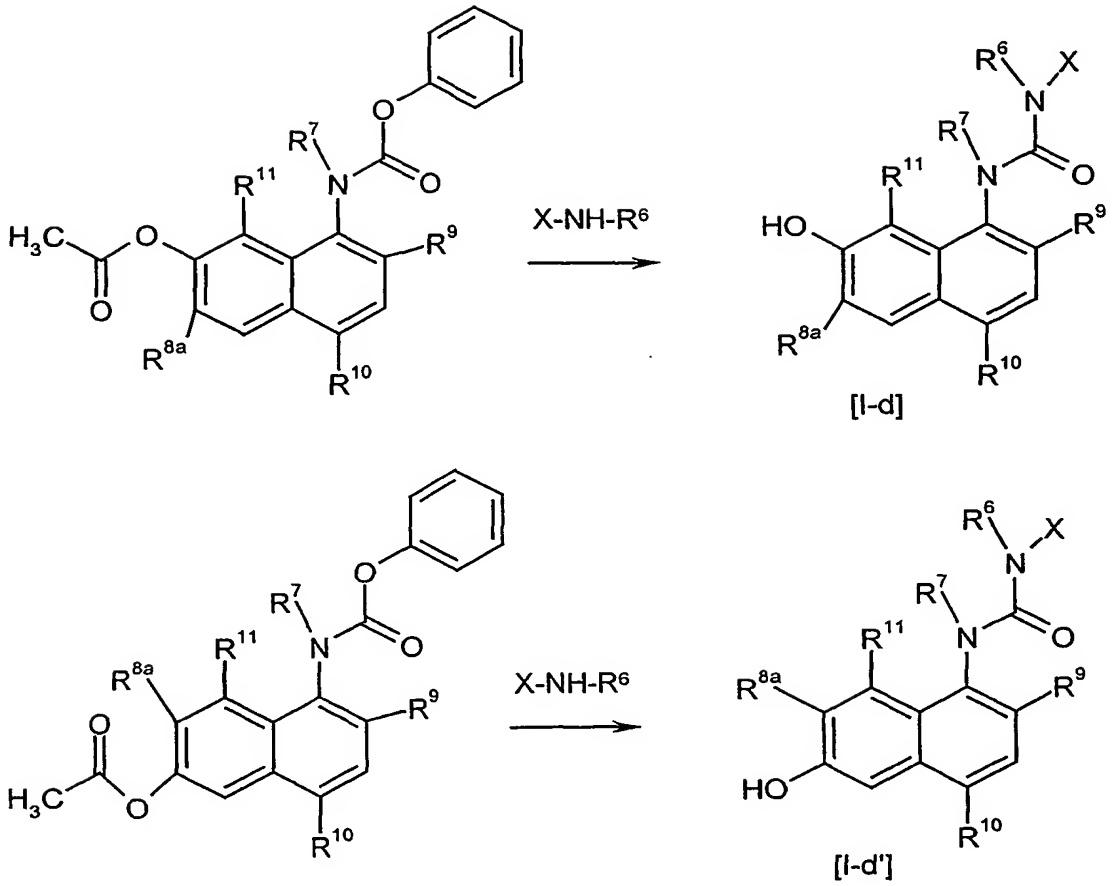
[1-c']

The compound [I-c] and the compound [I-c'], wherein R^6, R^7, R^{8a}, R^9, R^{10}, R^{11}, and X are the same as defined above, can be prepared by the reaction of a substituted naphthylamine carbamate and amine represented by the formula X-NH-R^6 (wherein R^6 and X are the same as defined above). The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 1 hour to 48 hours and preferably 2 to 24 hours.

The substituted naphthylamine carbamate and amine are commercially available or can be prepared by the use of known techniques.

[Method D]



The compound [I-d] and the compound [I-d'], wherein R^6, R^7, R^{8a}, R^9, R^{10}, R^{11}, and X are the same as defined above, can be prepared by (1) reacting a substituted naphthylamine carbamate and amine represented by the formula X-NH-R^6 (wherein R^6 and X are the same as defined above), and (2) adding base to the reaction mixture. The reaction (1) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide

(DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 1 hour to 48 hours and preferably 2 to 24 hours.

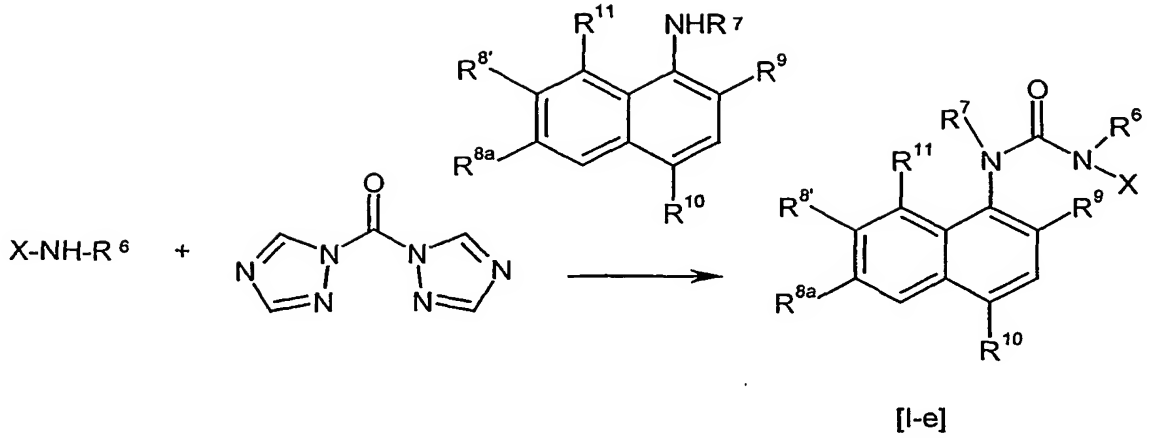
The reaction (2) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohol such as tert-butanol, methanol and ethanol; water, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 30°C to 100°C. The reaction may be conducted for, usually, 1 hour to 48 hours and preferably 2 to 24 hours.

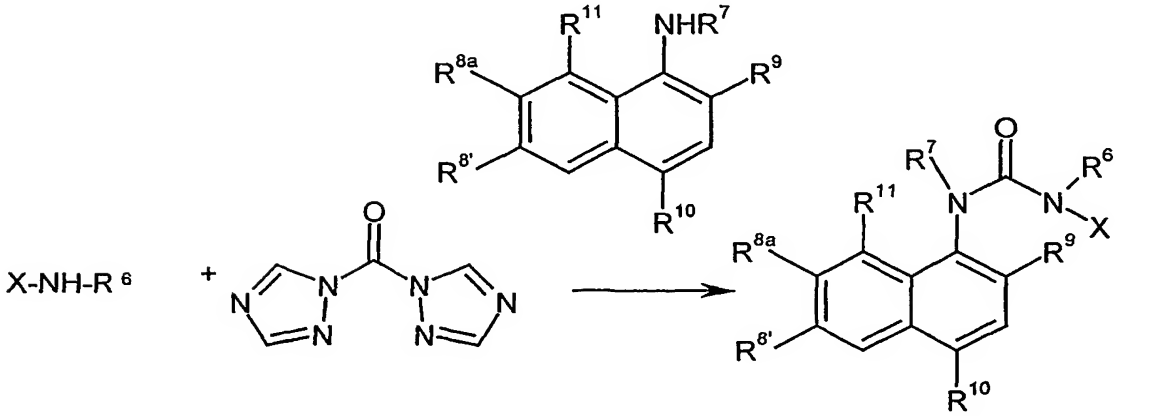
The base used in the reaction (2) can be, for instance, alkali metal alkoxide such as sodium methoxide and sodium ethoxide; alkali metal hydroxide such as sodium hydroxide and potassium hydroxide, and others.

The substituted naphthylamine carbamate and amine are commercially available or can be prepared by the use of known techniques.

[Method E]



[I-e]



[I-e']

The compound [I-e] and the compound [I-e'], wherein R^7, $R^{8'}$, R^{8a}, R^9, R^{10}, R^{11}, and X are the same as defined above, can be prepared by (1) reacting amine represented by the formula X-NH-R^6 (wherein R^6 and X are the same as defined above) and 1,1'-carbonyldi(1,2,4-triazole) (CDT) and (2) adding substituted naphthylamine to the reaction mixture. The reaction (1) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-

dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

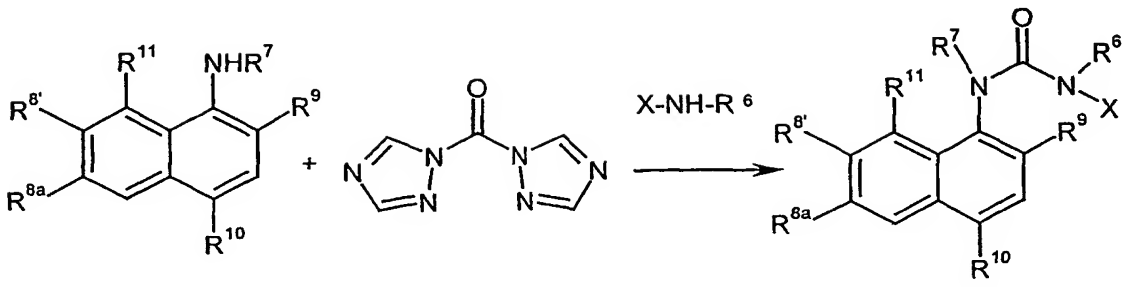
The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 40 hours and preferably 1 to 24 hours.

The reaction (2) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

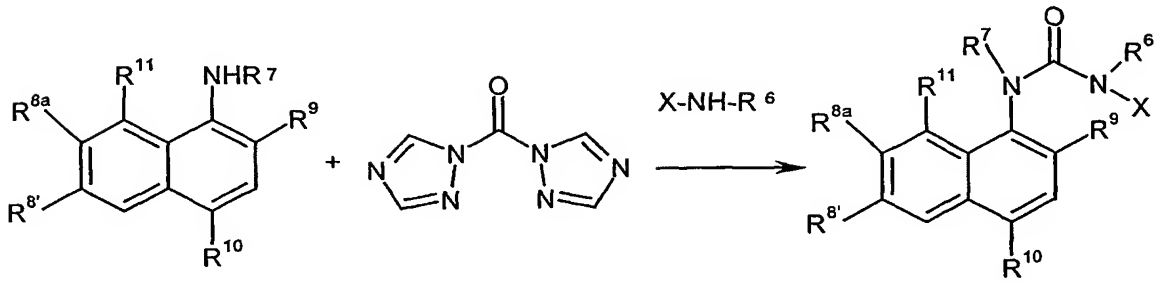
The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 30°C to 100°C. The reaction may be conducted for, usually, 1 hour to 48 hours and preferably 2 to 24 hours.

The amine, 1,1'-carbonyldi(1,2,4-triazole) (CDT) and substituted naphthylamine are commercially available or can be prepared by the use of known techniques.

[Method F]



[I-f]



[I-f']

The compound [I-f] and the compound [I-f'], wherein R^6, R^7, $R^{8'}$ R^{8a}, R^9, R^{10}, R^{11} and X is the same as defined above, can be prepared by (1) reacting a substituted naphthylamine and 1,1'-carbonyldi(1,2,4-triazole) (CDT), and (2) adding amine represented by the formula X-NH-R^6 (wherein R^6 and X are the same as defined above) to the reaction mixture. The reaction (1) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on The reaction temperature can be optionally set depending on the compounds to be reacted. The

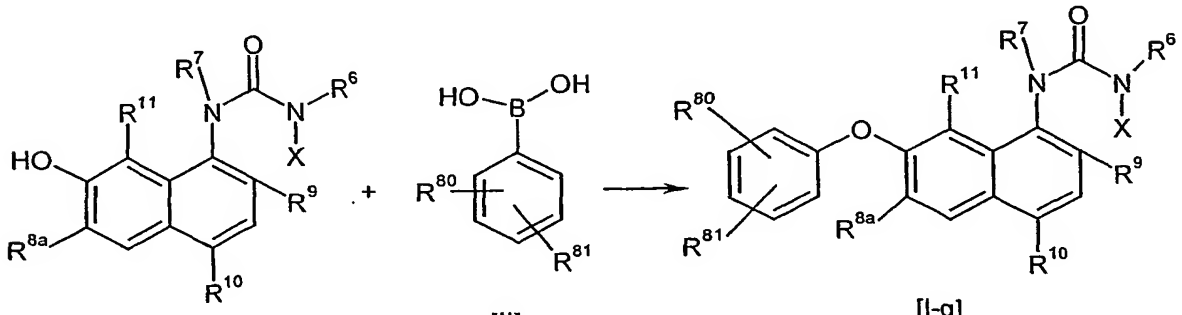
reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The reaction (2) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

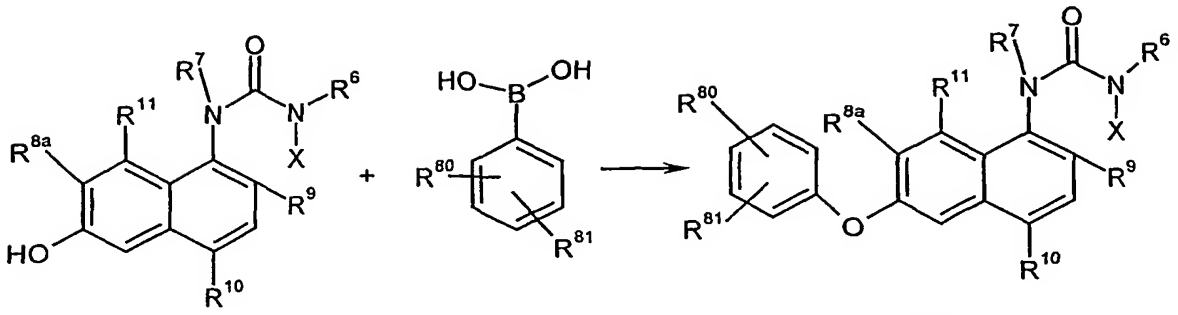
The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 1 hour to 48 hours and preferably 2 to 24 hours.

The substituted naphthylamine, 1,1'-carbonyldi(1,2,4-triazole) (CDT) and amine are commercially available or can be prepared by the use of known techniques.

[Method G]



[II] [I-g]



[II] [I-g']

The compound [I-g] and compound [I-g']wherein X, R^6, R^7, R^9, R^{10}, and R^{11} are the same as defined above and; R^{80} and R^{81} are identical or different and represent hydrogen, halogen, or C_{1-6} alkoxy, can be, but not limited to be, prepared by reacting substituted naphthyl amine with an arylboronic acid [II], wherein R^{80} and R^{81} are the same as defined above.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

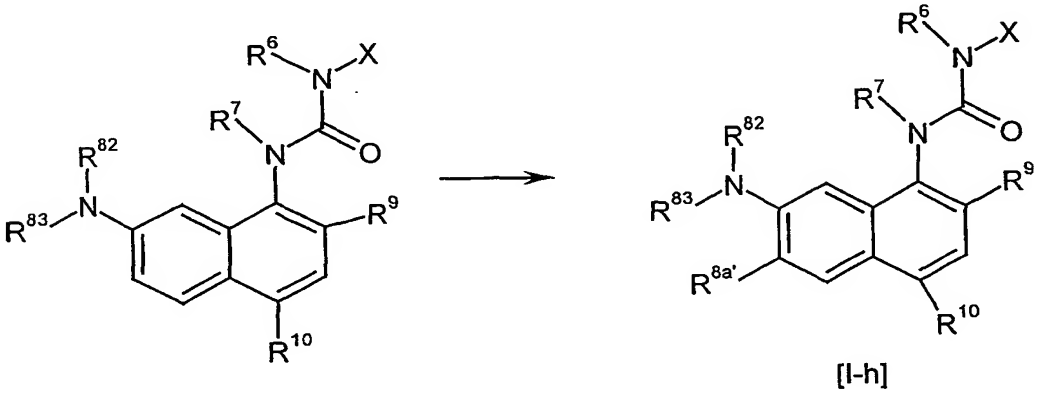
The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 40 hours and preferably 1 to 24 hours.

The reaction can be advantageously conducted in the presence of substance having catalytic activity. Such substances include, but not limited to, copper salts, such as copper (II) acetate, or the like.

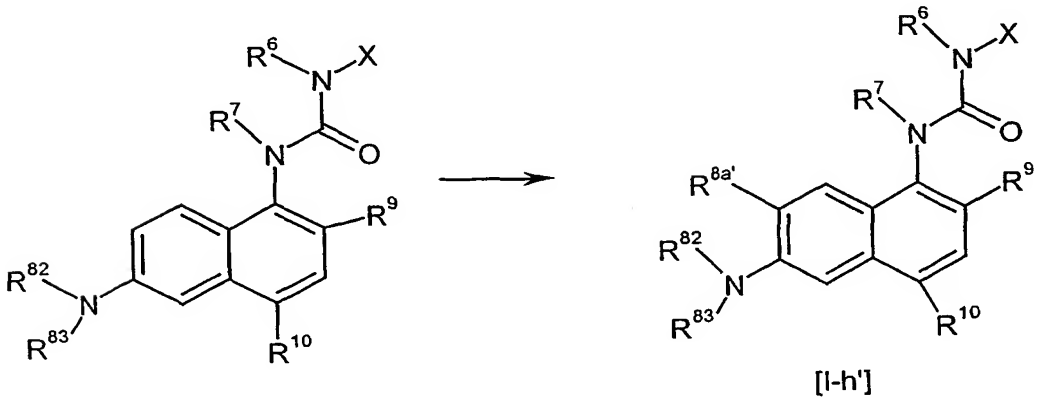
The reaction can also be advantageously carried out in the presence of a base including, for instance, organic amines such as triethylamine and N,N-diiso-propylethylamine, and the others.

The arylboronic acid and coper salts are commercially available or can be prepared by the use of known techniques.

[Method H]



[I-h]



[I-h']

The compound [I-h] and the compound [I-h'], wherein R^{82} is hydrogen, or straight-chain or branched C_{1-6} alkyl, R^{83} is hydrogen, straight-chain or branched C_{1-6} alkyl, or phenyl C_{1-6} alkyl, $R^{8a'}$ is halogen, R^9, R^{10} and X are the same as defined above, can be prepared by reacting a substituted naphthylamine and suitable halogenating

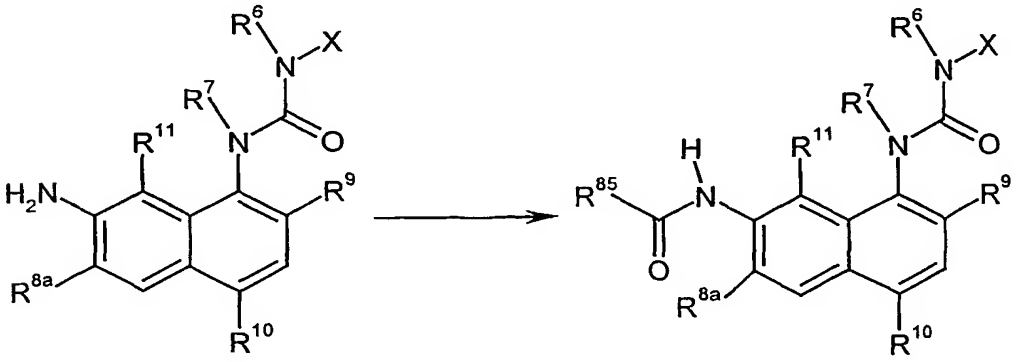
agents, for instance, N-halosuccinimides such as N-chlorosuccinimide and N-bromo-succinimide; and N-fluoro-pyridium salts such as N-fluoro-4-methylpyridinium-2-sulfonate, and others.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

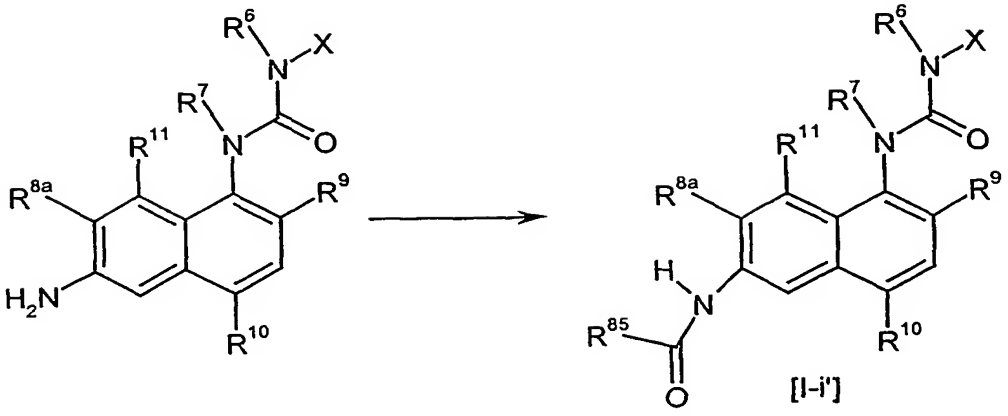
The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 60°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The substituted naphthylamine and halogenating agents are commercially available or can be prepared by the use of known techniques.

[Method I]



[I-i]



[I-i']

The compound [I-i] and the compound [I-i'], wherein R^{85} represents hydrogen or straight-chain or branched C_{1-6} alkyl and R^6, R^7, R^{8a}, R^9, R^{10}, R^{11} and X is the same as defined above, can be prepared by reacting a substituted naphthylamine and suitable acylating agents, for instance, carboxylic anhydrides such as formic anhydride, and acetic anhydride; acyl halides such as acetyl chloride, and others.

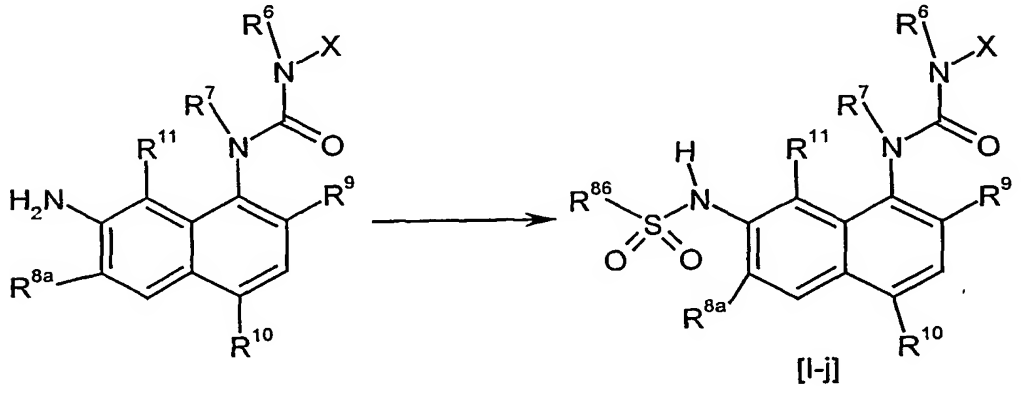
The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction can be advantageously carried out in the presence of a base including, for instance, alkali metal carbonates such as sodium carbonate and potassium carbonate; alkali metal hydrogen carbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, and others.

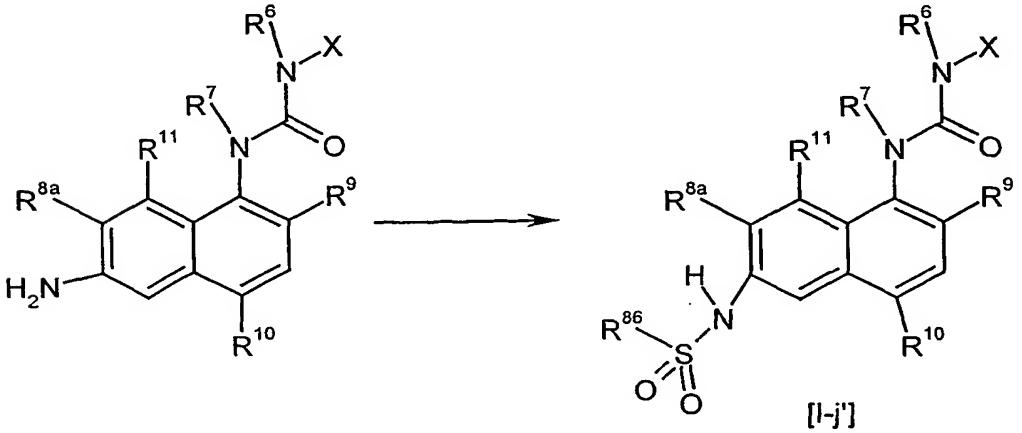
The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 10 hours.

The substituted naphthylamine and acylating agents are commercially available or can be prepared by the use of known techniques.

[Method J]



[I-j]



[I-j']

The compound [I-j]and the compound [I-j'], wherein R^{86} is straight-chain or branched C_{1-6} alkyl and R^6, R^7, R^{8a}, R^9, R^{10}, R^{11} and X is the same as defined above, can be prepared by reacting a substituted naphthylamine and alkylsulfonyl chloride such as methanesulfonyl chloride, ethanesulfonyl chloride and others.

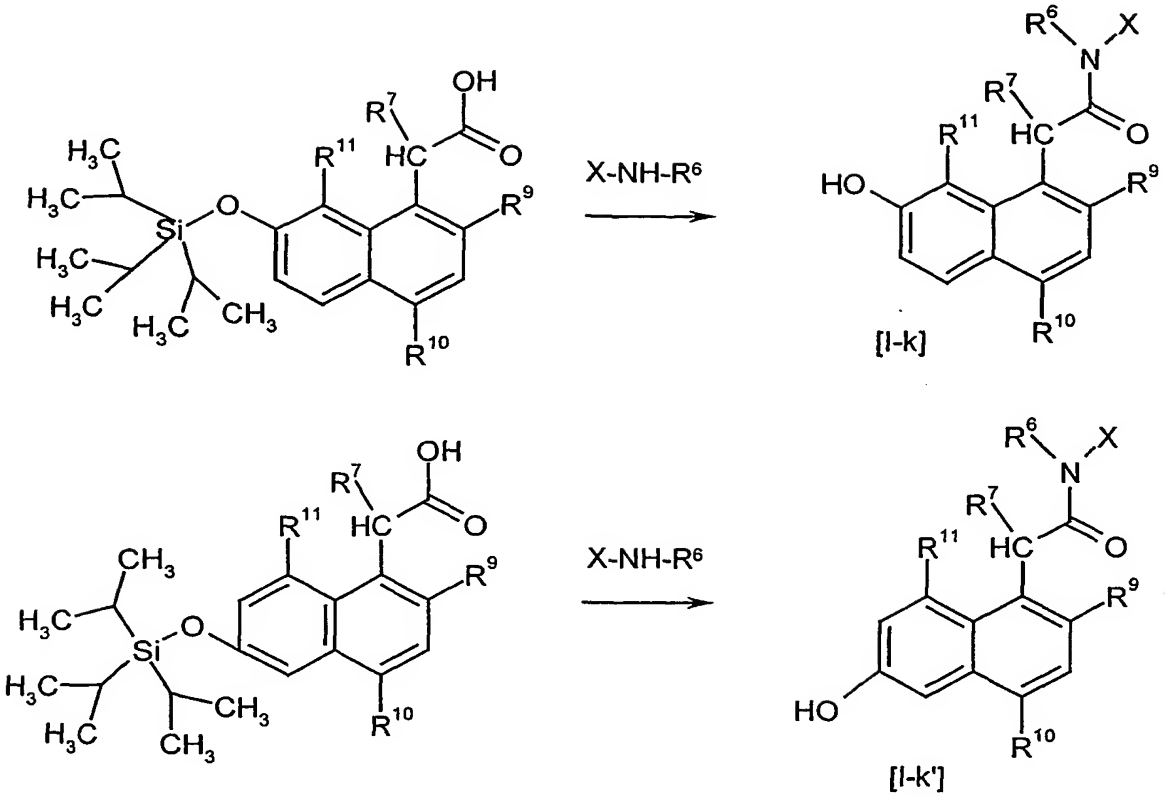
The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction can be advantageously carried out in the presence of a base including, for instance, alkali metal carbonates such as sodium carbonate or potassium carbonate; alkali metal hydrogen carbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The substituted naphthylamine and alkylsulfonyl chlorides are commercially available or can be prepared by the use of known techniques.

[Method K]



The compound [I-k] and the compound [I-k'], wherein R^6, R^7, R^9, R^{10}, R^{11}, and X are the same as defined above, can be prepared by (1)the reacting a substituted naphthalene and amine represented by the formula X-NH-R^6 (wherein R^6 and X are the same as defined above) (2) adding fluoride salts, such as tetrabutylamonium fluoride to the reaction mixture.

The reaction (1) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction may be carried out using coupling agent including, for instance, carbodiimides such as N, N-dicyclohexylcarbodiimide and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide, and others.

The reaction may be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, 4-dimethlyaminopyridine, triethyl-amine and N,N-diisopropylethylamine, and others.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 60°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

The reaction (2) may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethylether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; ketones such as acetone; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The substituted naphthalene, amine, and fluoride salt are commercially available or can be prepared by the use of known techniques.

When the compound shown by the formula (I) or a salt thereof has tautomeric isomers and/or stereoisomers (e.g., geometrical isomers and conformational isomers), each of their separated isomer and mixtures are also included in the scope of the present invention.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or

hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the

compounds of the invention together with one or more pharmaceutically-acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 presents charts showing bladder capacity and voiding frequency in normal rats, cyclophosphamide treated rats (vehicle) and CYP-VR1 antagonist treated rats.

Fig. 2 presents graphs which shows the bladder capacity in normal rats, cyclophosphamide treated rats (vehicle), and CYP-VR1 antagonist treated rats.

Fig. 3 presents graphs which shows the micturition frequency in normal rats, cyclophosphamide treated rats (vehicle), and CYP-VR1 antagonist treated rats.

EMBODIMENT OF THE INVENTION

EXAMPLES

The present invention will be described as a form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Mass spectra were obtained using electrospray (ES) ionization techniques (micromass Platform LC). Melting points are uncorrected. Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column (4.6 mmϕ X 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe

Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KgaA, Kanto Chemical Co.,Ltd.

The effect of the present compounds were examined by the following assays and pharmacological tests.

[Measurement of capsaicin-induced Ca^{2+} influx in the human VR1-transfected CHO cell line] (Assay 1)

(1) Establishment of the human VR1-CHOluc9aeq cell line

Human vanilloid receptor (hVR1) cDNA was cloned from libraries of axotomized dorsal root ganglia (WO2000/29577). The cloned hVR1 cDNA was constructed with pcDNA3 vector and transfected into a CHOluc9aeq cell line. The cell line contains aequorin and CRE-luciferase reporter genes as read-out signals. The transfectants were cloned by limiting dilution in selection medium (DMEM/F12 medium (Gibco BRL) supplemented with 10% FCS, 1.4 mM Sodium pyruvate, 20 mM HEPES, 0.15% Sodium bicarbonate, 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM glutamine, non-essential amino acids and 2 mg/ml G418). Ca^{2+} influx was examined in the capsaicin-stimulated clones. A high responder clone was selected and used for further experiments in the project. The human VR1-CHOluc9aeq cells were maintained in the selection medium and passaged every 3-4 days at 1-2.5x10^5 cells/flask (75 mm^2).

(2) Measurement of Ca^{2+} influx using FDSS-3000

Human VR1-CHOluc9aeq cells were suspended in a culture medium which is the same as the selection medium except for G418 and seeded at a density of 1,000 cells per well into 384-well plates (black walled clear-base / Nalge Nunc International). Following the culture for 48 hrs the medium was

changed to 2 μM Fluo-3 AM (Molecular Probes) and 0.02% Pluronic F-127 in assay buffer (Hank's balanced salt solution (HBSS), 17 mM HEPES (pH7.4), 1 mM Probenecid, 0.1% BSA) and the cells were incubated for 60 min at 25°C. After washing twice with assay buffer the cells were incubated with a test compound or vehicle for 20 min at 25°C. Mobilization of cytoplasmic Ca^{2+} was measured by FDSS-3000 (λ_{ex}=488nm, λ_{em}=540nm / Hamamatsu Photonics) for 60 sec after the stimulation with 10 nM of capsaicin (Nacalai Tesque). Integral R of the fluorescence changes was calculated in the samples treated with a test compound and vehicle respectively. Inhibitory effect of the compound was calculated by a comparison of the integral R values.

[Measurement of the capsaicin-induced Ca^{2+} influx in primary cultured rat dorsal root ganglia neurons] (Assay 2)

(1) Preparation of rat dorsal root ganglia neurons

New born Wister rats (5-11 days) were sacrificed and dorsal root ganglia (DRG) was removed. DRG was incubated with 0.1% trypsin (Gibco BRL) in PBS(-) (Gibco BRL) for 30 min at 37°C, then a half volume of fetal calf serum (FCS) was added and the cells were spun down. The DRG neuron cells were resuspended in Ham F12/5% FCS/5% horse serum (Gibco BRL) and dispersed by repeated pipetting and passing through 70 μm mesh (Falcon). The culture plate was incubated for 3 hours at 37°C to remove contaminating Schwann cells. Non-adherent cells were recovered and further cultured in laminin-coated 384 well plates (Nunc) at $1x10^4$ cells/50 μl/well for 2 days in the presence of 50 ng/ml recombinant rat NGF (Sigma) and 50 μM 5-fluorodeoxyuridine (Sigma).

(2) Ca^{2+} mobilization assay

DRG neuron cells were washed twice with HBSS supplemented with 17 mM HEPES (pH 7.4) and 0.1% BSA. After incubating with 2 μM fluo-3AM (Molecular Probe), 0.02% PF127 (Gibco BRL) and 1 mM probenecid (Sigma) for 40 min at 37°C, cells were washed 3 times. The cells were incubated with VR1 antagonists or vehicle (dimethylsulphoxide) and then with 1 μM of capsaicin (Nacalai Tesque) in FDSS-6000 (λ_{ex}=480nm, λ_{em}=520nm / Hamamatsu Photonics). The fluorescence changes at 480nm were monitored for 2.5 min. Integral R of the fluorescence change was calculated in the samples treated with a compound and vehicle, respectively. Inhibitory effect of the compound was calculated by comparison of the integral R-values.

[Organ bath assay to measure the capsaicin-induced bladder contraction] (Assay 3)

Male Wistar rats (10 week old) were anesthetized with ether and sacrificed by dislocating the necks. The whole urinary bladder was excised and placed in oxygenated Modified Krebs-Henseleit solution (pH 7.4) of the following composition (112mM NaCl, 5.9mM KCl, 1.2mM $MgCl_2$, 1.2mM NaH_2PO_4, 2mM $CaCl_2$, 2.5mM $NaHCO_3$, 12mM glucose). Contractile responses of the urinary bladder were studied as described previously [Maggi CA et al: Br.J.Pharmacol. 108: 801-805, 1993]. Isometric tension was recorded under a load of 1 g using longitudinal strips of rat detrusor muscle. Bladder strips were equilibrated for 60 min before each stimulation. Contractile response to 80 mM KCl was determined at 15 min intervals until reproducible responses were obtained. The response to KCl was used as an internal standard to evaluate the maximal response to capsaicin. The effects of the compounds were investigated by incubating the strips with compounds for 30 min prior to the stimulation with 1 μM of capsaicin (Nacalai Tesque) (vehicle: 80% saline, 10% EtOH, and 10% Tween 80). One of the preparations made from the same animal was served as a control while the others were used for evaluating compounds. Ratio of each capsaicin-induced contraction to the internal standard (i.e.

KCl-induced contraction) was calculated and the effects of the test compounds on the capsaicin-induced contraction were evaluated.

[Measurement of capsaicin-induced over active bladder contraction in anesthetized rats] (Assay 4)

(1) Animals

Female Sprague-Dawley rats (180~250 g / Charles River Japan) were used.

(2) Catheter implantation

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.2 g/kg. The abdomen was opened through a midline incision, and a polyethylene catheter (BECTON DICKINSON, PE50) was implanted into the bladder through the dome. In parallel, the inguinal region was incised, and a polyethylene catheter (Hibiki, size 5) filled with 2 IU / ml of heparin (Novo Heparin, Aventis Pharma, France) in saline (Otsuka) was inserted into a femoral vein.

(3) Cystometric investigation

The bladder catheter was connected via T-tube to a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) and a microinjection pump (TERUMO). Saline was infused at room temperature into the bladder at a rate of 3.6 ml/hr. Intravesical pressure was recorded continuously on a chart pen recorder (Yokogawa). At least three reproducible micturition cycles, corresponding to a 20-minute period, were recorded before a test compound administration and used as baseline values.

(4) Administration of test compounds and stimulation of bladder with capsaicin

The saline infusion was stopped before administrating compounds. A testing compound dissolved in the mixture of ethanol, Tween 80 (ICN Biomedicals Inc.) and saline (1 : 1 : 8, v/v/v) was administered intraarterially at 3mg/kg or 10 mg/kg. 2min after the administration of the compound, saline including 30 μM of capsaicin (Nacalai Tesque) was infused at room temperature into the bladder at a rate of 3.6 ml/hr.

(5) Analysis of cystometry parameters

Relative increases in the capsaicin-induced intravesical pressure were analyzed from the cystometry data. The capsaicin-induced bladder pressures were compared with the maximum bladder pressure during micturition without the capsaicin stimulation. The testing compounds–mediated inhibition of the increased bladder pressures was evaluated using Student's t-test. A probability level less than 5% was accepted as significant difference.

[Measurement of over active bladder in anesthetized cystitis rats] (Assay 5)

(1) Animals

Female Sprague-Dawley rats (180~250 g / Charles River Japan) were used. Cyclophosphamide (CYP) dissolved in saline was administered intra-peritoneally at 150 mg/kg 48 hours before experiment.

(2) Catheter implantation

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.25 g/kg. The abdomen was opened through a midline incision, and a polyethylene catheter (BECTON DICKINSON, PE50) was implanted into the

bladder through the dome. In parallel, the inguinal region was incised, and a polyethylene catheter (BECTON DICKINSON, PE50) filled with saline (Otsuka) was inserted into a femoral vein. After the bladder was emptied, the rats were left for 1 hour for recovery from the operation.

(3) Cystometric investigation

The bladder catheter was connected via T-tube to a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) and a microinjection pump (TERUMO). Saline was infused at room temperature into the bladder at a rate of 3.6 ml/hr for 20 min. Intravesical pressure was recorded continuously on a chart pen recorder (Yokogawa). At least three reproducible micturition cycles, corresponding to a 20-minute period, were recorded before a test compound administration.

(4) Administration of test compounds

A testing compound dissolved in the mixture of ethanol, Tween 80 (ICN Biomedicals Inc.) and saline (1 : 1 : 8, v/v/v) was administered intravenously at 0.05 mg/kg, 0.5 mg/kg or 5 mg/kg. 3min after the administration of the compound, saline (Nacalai Tesque) was infused at room temperature into the bladder at a rate of 3.6 ml/hr.

(5) Analysis of cystometry parameters

The cystometry parameters were analyzed as described previously [Lecci A et al: Eur. J. Pharmacol. 259: 129-135, 1994]. The micturition frequency calculated from micturition interval and the bladder capacity calculated from a volume of infused saline until the first micturition were analyzed from the cystometry data. The testing compounds–mediated inhibition of the frequency and the testing compounds–mediated increase of bladder capacity were

evaluated using unpaired Student's t-test. A probability levels less than 5% was accepted as significant difference. Data were analyzed as the mean ± SEM from 4 – 7 rats.

SELECTIVITY TEST

[Measurement of Ca^{2+} influx in the human P2X1-transfected CHO cell line]

(1) Preparation of the human P2X1-transfected CHOluc9aeq cell line

Human P2X1-transfected CHOluc9aeq cell line was established and maintained in Dulbecco's modified Eagle's medium (DMEM/F12) supplemented with 7.5% FCS, 20 mM HEPES-KOH (pH 7.4), 1.4 mM sodium pyruvate, 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM glutamine (Gibco BRL) and 0.5 Units/ml apyrase (grade I, Sigma). The suspended cells were seeded in each well of 384-well optical bottom black plates (Nalge Nunc International) at 3 x 10^3 / 50 μl / well. The cells were cultured for following 48 hrs to adhere to the plates.

(2) Measurement of the intracellular Ca^{2+} levels

P2X1 receptor agonist-mediated increases in cytosolic Ca^{2+} levels were measured using a fluorescent Ca^{2+} chelating dye, Fluo-3 AM (Molecular Probes). The plate-attached cells were washed twice with washing buffer (HBSS, 17 mM HEPES-KOH (pH 7.4), 0.1% BSA and 0.5 units/ml apyrase), and incubated in 40 μl of loading buffer (1 μM Fluo-3 AM, 1 mM probenecid, 1 μM cyclosporin A, 0.01% pluronic (Molecular Probes)in washing buffer) for 1 hour in a dark place. The plates were washed twice with 40 μl washing buffer and 35 μl of washing buffer were added in each well with 5 μl of test compounds or *2',3'-o*-(2,4,6-trinitrophenyl) adenosine 5'-triphosphate (Molecular Probes) as a reference. After further incubation for

10 minutes in dark 200 nM α,β-methylene ATP agonist was added to initiate the Ca^{2+} mobilization. Fluorescence intensity was measured by FDSS-6000 (λ_{ex}=410nm, λ_{em}=510nm / Hamamatsu Photonics) at 250 msec intervals. Integral ratios were calculated from the data and compared with that of a control.

All of the compounds in the examples were examined in the assays.

The data corresponds to the compounds as yielded by solid phase synthesis and thus to levels of purity of about 40 to 90%. Almost all of the compounds (more than 95% of the compounds) disclosed in the Examples below and tables below show IC_{50} value of equal or below 1μM. Among others, the following compounds:

N-(7-hydroxy-1-naphthyl)-N'-[4-(trifluoromethyl)phenyl]urea;

N-(7-hydroxy-1-naphthyl)-N'-(4-phenoxyphenyl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7-hydroxy-1-naphthyl)urea;

N-[4-(4-chlorophenoxy)phenyl]-N'-(7-hydroxy-1-naphthyl)urea;

N-(1,1'-biphenyl-3-yl)-N'-(7-hydroxy-1-naphthyl)urea;

N-(7-hydroxy-1-naphthyl)-N'-(3-phenoxyphenyl)urea;

N-(3-chlorophenyl)-N'-(2,4-dibromo-7-hydroxy-1-naphthyl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(2,4-dibromo-7-hydroxy-1-naphthyl)urea;

N-(4-bromobenzyl)-N'-(2-chloro-7-hydroxy-1-naphthyl)urea;

N-(2-chloro-7-hydroxy-1-naphthyl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(2,4-dichloro-7-hydroxy-1-naphthyl)urea;

N-(1,1'-biphenyl-3-yl)-N'-(2-chloro-7-hydroxy-1-naphthyl)urea;

ethyl 3-({[(2,4-dichloro-7-hydroxy-1-naphthyl)amino]carbonyl}amino)benzoate;

N-(2,4-dichloro-7-hydroxy-1-naphthyl)-N'-(2-naphthyl)urea;

N-(2,4-dichloro-7-hydroxy-1-naphthyl)-N'-[3-(trifluoromethyl)phenyl]urea;

N-(2'-chloro-1,1'-biphenyl-3-yl)-N'-(2,4-dichloro-7-hydroxy-1-naphthyl)urea;

N-(4-bromo-2-chloro-7-hydroxy-1-naphthyl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea;

N-(2,4-dichloro-7-hydroxy-1-naphthyl)-N'-[4-fluoro-3-(trifluoromethyl)phenyl]urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7-hydroxy-4-methyl-1-naphthyl)urea; and

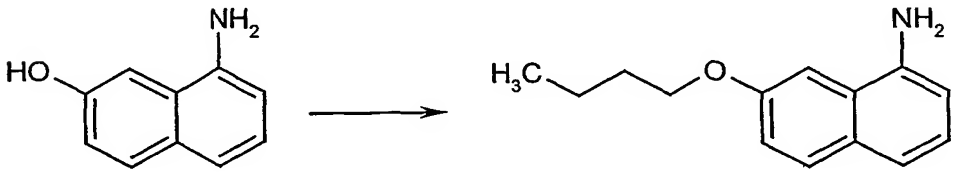
N-(2-chloro-7-hydroxy-4-methyl-1-naphthyl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea

or the salt thereof (e.g., potassium salt) show IC_{50} value of equal to or below 10 nM.

The compounds of the present invention also show excellent selectivity, and strong activity in other assays (2)-(4) described above.

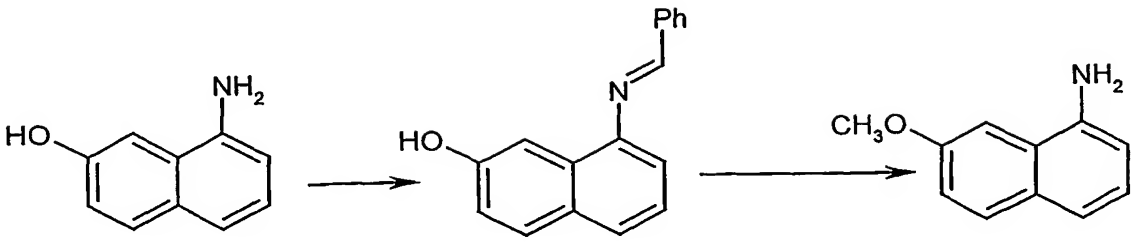
Preparing method of starting compounds

[Starting compound A]



To a stirred solution of 8-amino-2-naphthol (0.050 g, 0.314 mmol), tetrabutylammonium iodide (0.012 g, 0.031 mmol) and 1-bromobutane (0.04 mL, 0.346 mmol) in acetone (2 mL) was added potassium carbonate (0.130 g, 0.942 mmol). The mixture was stirred at room temperature for one day, then warm to 60°C for one day and diluted with AcOEt. The mixture was extracted with ethyl acetate and water. Then the layers are separated. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography on silica gel (hexane / ethyl acetate = 4/1) to give 7-butoxy-1-naphthylamine (0.040 g, 59%).

[Starting compound B]

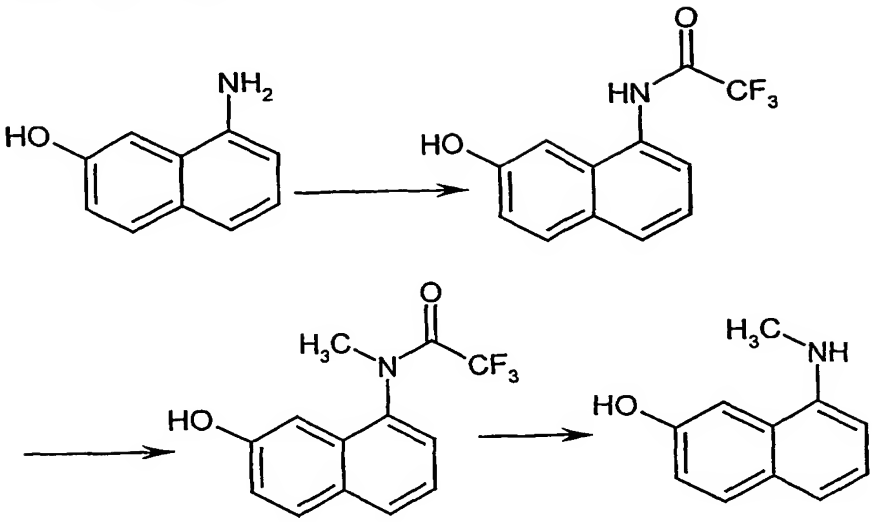


A mixture of 8-amino-2-naphthol (1.0 g, 6.28 mmol), benzaldehyde (0.73 g, 6.91 mmol) and Na_2SO_4 (5.0 g, 35.20 mmol) in boiling THF (12 ml) was stirred overnight. The mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (Hex / AcOEt / Et_3N = 75/ 23/2) to give 8-{[(1E)-phenylmethylidene]amino}-2-naphthol (1.52 g, yield 98%) as a yellow solid.

Next, A mixture of 8-{[(1E)-phenylmethylidene]amino}-2-naphthol (0.50 g, 2.02 mmol), MeI (0.57 g, 4.04 mmol), and NaOH (0.24 g, 6.06 mmol) in acetone was stirred at room temperature for 2 hrs. The resulting mixture was concentrated, and the residue was dissolved in Et_2O, washed with water and brine and then concentrated under reduced pressure. The residue was dissolved in 2N HCl-THF (30 ml, 2 : 1) and stirred at room temperature for 1.5 hrs. The resulting solution was washed with Et_2O. The aqueous layer was basified with Na_2CO_3, extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (Hex / AcOEt = 3 / 1) to give 7-methoxy-1-naphthylamine (0.33 g 93%) as a white solid.

With the use of EtI, iPrBr, or Bromomethyl-cyclopropane instead of MeI, 7-ethoxy-1-naphthylamine, 7-propyl-1-naphthylamine, or 7-(cyclopropylmethoxy)-1-naphthyl-amine, was prepared, respectively.

[Starting compound C]

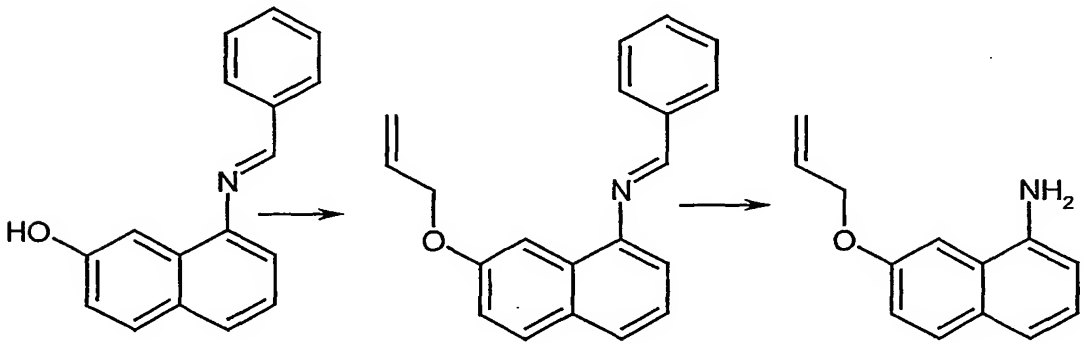


To a solution of 8-amino-2-naphthol (10.62 g, 62.82 mmol) and pyridine (9.94 g, 125.64 mmol) in dry dioxane (300 ml) was added at 0°C trifluoroacetic anhydride (19.79g, 94.23 mmol). The solution was allowed to warm to room temperature and stirred for 1.5 hrs. The resulting solution was concentrated. The residue was dissolved in Et_2O, washed with 1N HCl and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (hexane : AcOEt = 6 : 1) to give 2,2,2-trifluoro-N-(7-hydroxy-1-naphthyl)acetamide (4.73g, 30%) as a purple solid.

Next, A mixture of 2,2,2-trifluoro-N-(7-hydroxy-1-naphthyl)acetamide (0.50 g, 1.96 mmol), MeI (0.31 g, 2.16 mmol), K_2CO_3 (1.35 g, 9.80 mmol) and TBAI (0.072 g, 0.196 mmol) in acetone (10 ml) was stirred at room temperature for 2.5 hrs. The resulting mixture was filtered and concentrated. The residue was diluted with AcOEt and washed with brine, dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gal (hexane / AcOEt = 10 / 1 then 4 / 1) to give 2,2,2-trifluoro-N-(7-hydroxy-1-naphthyl)-N-methylacetamide (0.33 g, 63%) as a white solid.

Next, To a solution of 2,2,2-trifluoro-N-(7-hydroxy-1-naphthyl)-N-methylacetamide (0.058 g, 0.22mmol) in EtOH (3 ml) was added $NaBH_4$ (0.15 g, 0.215 mmol). The reaction mixture was stirred at room temperature until TLC showed no starting material present. The solution was concentrated. The residue was dissolved in Et_2O, washed with H_2O and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (hexane / AcOEt = 4/ 1) to give 8-(methylamino)-2-naphthol (0.032 g, 87%) as a white solid.

[Starting compound D]

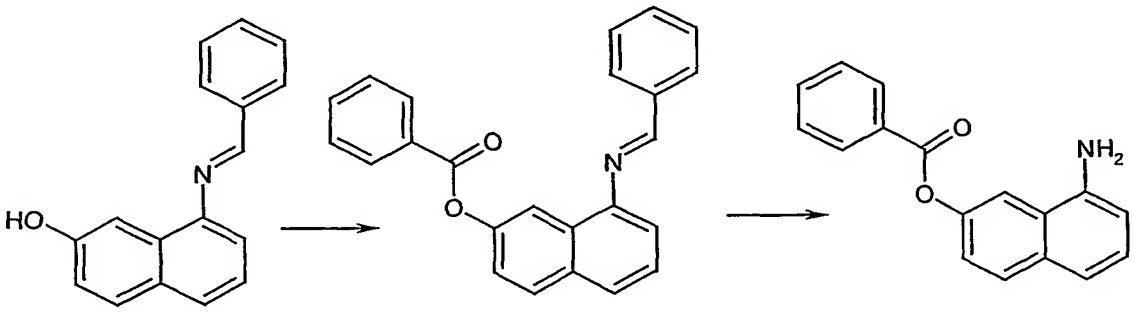


To a suspension of 8-{[(1E)-phenylmethylidene]amino}-2-naphthol, which was prepared in the step (1) of the process of preparing the starting compound B, (236 mg, 0.95 mmol) and K_2CO_3 (263 mg, 1.90 mmol) in 10 mL of DMF was added allylbromide (150 mg, 1.24 mmol) at room temperature. After 3hrs, the reaction mixture was poured into water (50mL) and extracted with Et_2O. The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc= 1/10) to give 7-(allyloxy)-N-[(1E)-phenylmethylidene]-1-naphthalenamine (259 mg, 95%) as a solid.

Next, obtained 7-(allyloxy)-N-[(1E)-phenylmethylidene]-1-naphthalenamine was dissolved in the mixture of THF and aqueous 2N HCl solution (20 mL, 1:3). After 1hr

stirring at room temperature, the solvent was removed under reduced pressure and the aqueous phase was extracted with Et_2O, and the organic layers was discarded. The aqueous phase was alkalized with aqueous 1N NaOH solution, and then the mixture was extracted with EtOAc. The EtOAc solution was dried over Na_2SO_4 and then concentrated under reduced pressure to give the crude product. Then the crude product was purified by column chromatography on silica gel(hexane/EtOAc= 1/8 then 1/5) to give 7-(allyloxy)-1-naphthylamine (128.5 mg, 66%) as a solid.

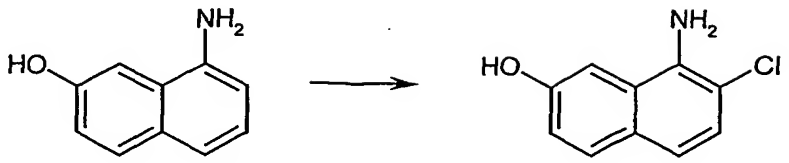
[Starting compound E]



To a mixture of 8-{[(1E)-phenylmethylidene]amino}-2-naphthol, which was prepared in the step (1) of the process of preparing starting compound B, (101 mg, 0.45 mmol), benzoyl chloride (70 mg, 0.50 mmol) in 20 mL of CH_2Cl_2 was added TEA (68 mg, 0.65 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1hr. After removal of the solvent, the residue was washed with hexane.

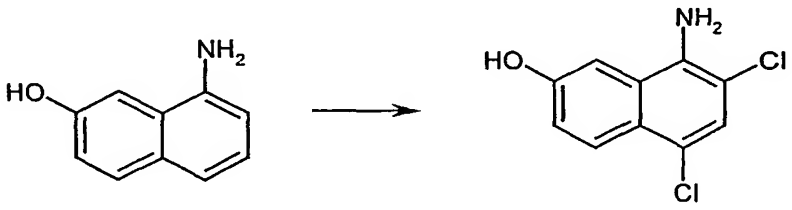
The obtained crude product was dissolved in a mixture of THF (5 mL) and aqueous 2N HCl solution (10 mL). After 1hr of stirring at room temperature, the solvent was removed in vacuo and the aqueous phase was extracted Et_2O, and the organic layer was discarded. The aqueous phase was alkalized with aqueous 1N NaOH solution and then the mixture was extracted with EtOAc. The EtOAc solution was dried over Na_2SO_4 and then concentrated under reduced pressure to give the crude product. Then the crude product was recrystallized from Et_2O to give 8-amino-2-naphthyl benzoate (108 mg, 92%) as a solid.

[Starting compound F]



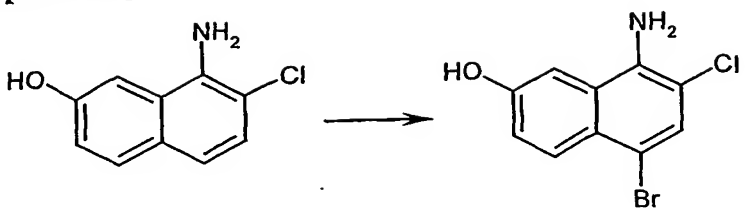
To a stirred solution of 8-amino-2-naphthol (5.00 g, 31.4 mmol) in tetrahydrofuran (100 mL) was added n-chlorosuccinimide (4.19 g, 31.4 mmol). The mixture was stirred at room temperature for 16 hours. Water was added to the mixture, and the product was extracted with ethylacetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 8-amino-7-chloro-2-naphthol (4.2 g, 69 % yield).

[Starting compound G]



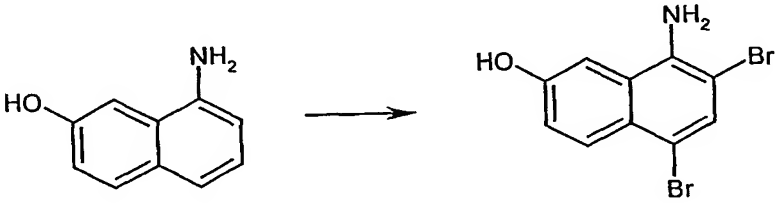
To a stirred solution of 8-amino-2-naphthol(2.00 g, 12.6 mmol) in tetrahydrofuran (50 mL) was added N-chlorosuccinimide (3.69 g, 27.6 mmol). The mixture was stirred at room temperature for 16 hours. Water was added to the mixture, and the product was extracted with ethylacetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 8-amino-5,7-dichloro-2-naphthol (2.0 g, 70 % yield).

[Starting compound H]



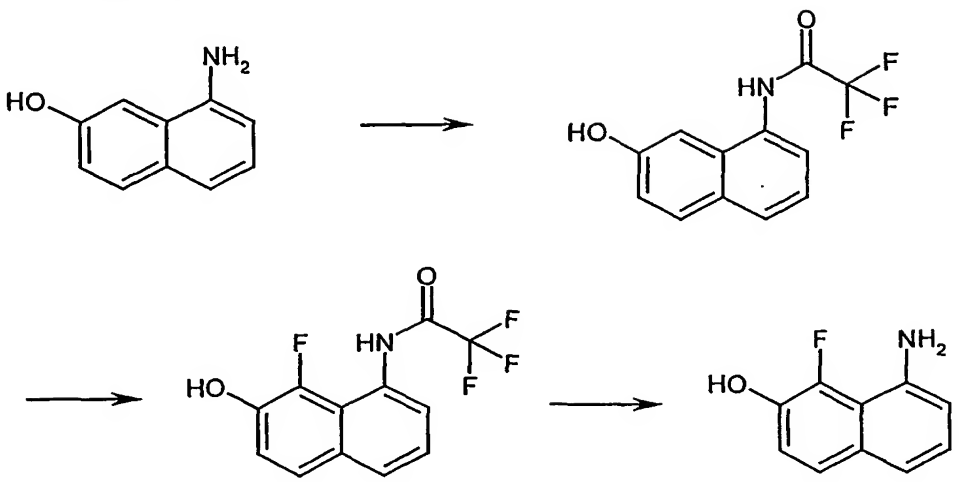
To a stirred solution of 8-amino-7-chloro-2-naphthol (500 mg, 2.58 mmol) in tetrahydrofuran (8 mL) was added N-bromosuccinimide (460 mg, 2.58 mmol). The mixture was stirred at room temperature for 16 hours. Water was added to the mixture, and the product was extracted with ethylacetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 8-amino-5-bromo-7-chloro-2-naphthol (289 mg, 41 % yield).

[Starting compound I]



To a stirred solution of 8-amino-2-naphthol (10.0 g, 62.8 mmol) in tetrahydrofuran (300 mL) was added N-bromosuccinimide (22.4 g, 126 mmol) at 0°C. The mixture was stirred at room temperature for 16 hours. Water was added to the mixture, and the product was extracted with ethylacetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 8-amino-5,7-dibromo-2-naphthol (5.1 g, 26 % yield).

[Starting compound J]

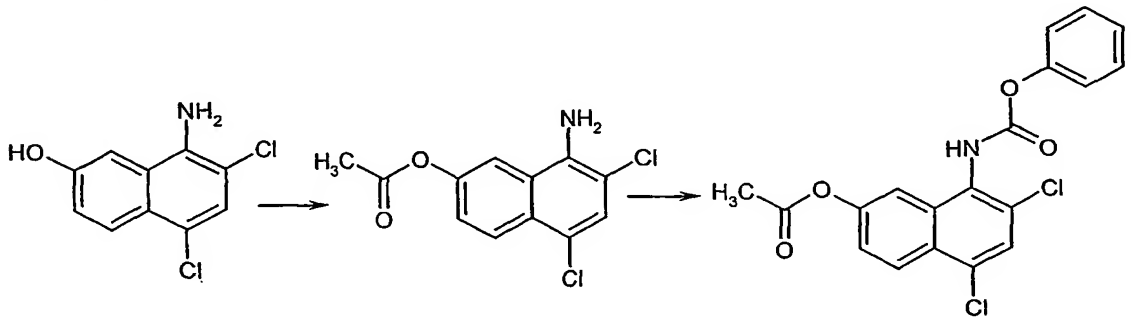


To a solution of 8-amino-2-naphthol (1.59 g, 9.99 mmol) and pyridine (2 mL) in 1,4-dioxane (10 mL) was added trifluoroacetic anhydride (3.15 g, 15.0 mmol) in 1,4-dioxane (5 mL) at 0°C. After stirred for 16 hours, methanol (5 mL) was added and stirred for 5 minutes. An aqueous solution of 1N HCl was added to the mixture and the product was extracted with ethylacetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethylacetate, 3:1) to give 2,2,2-trifluoro-N-(7-hydroxy-1-naphthyl)acetamide (2.19 g, 86 % yield).

Next, a mixture of 2,2,2-trifluoro-N-(7-hydroxy-1-naphthyl)acetamide (500 mg, 1.96 mmol) and N-fluoro-6-(trifluoromethyl)pyridinium-2-sulfonate (504 mg, 2.06 mmol) in 1,1,2-trichloroethane (5 mL) was stirred at 50°C for 18 hours. The mixture was poured into water. The product was extracted with diethylether, and the organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatograpy (chloroform: methanol, 50:1) to give 2,2,2-trifluoro-N-(8-fluoro-7-hydroxy-1-naphthyl)acetamide (200 mg, 37 % yield).

Next, a solution of 2,2,2-trifluoro-N-(8-fluoro-7-hydroxy-1-naphthyl)acetamide (194 mg, 0.710 mmol) in saturated ammonia in methanol was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (hexane:ethylacetate, 2:1) to give 8-amino-1-fluoro-2-naphthol (119 mg, 95 % yield).

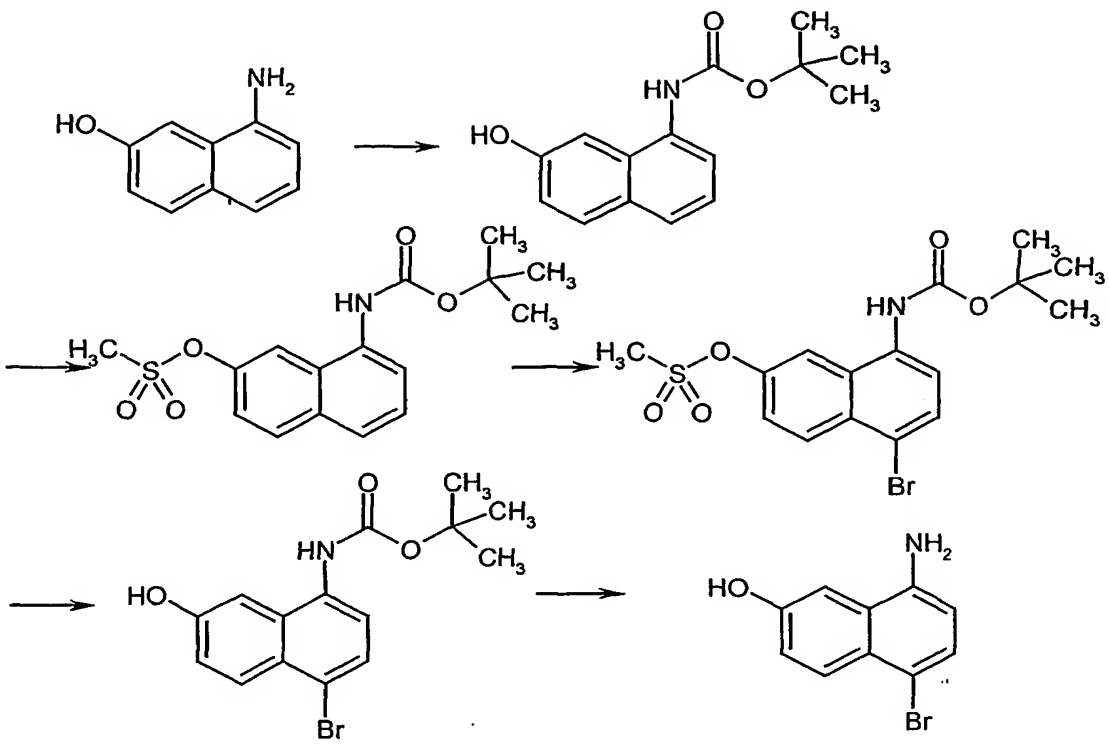
[Starting compound K]



To a solution of 8-amino-5,7-dichloro-2-naphthol (2.28 g, 10.0 mmol) and pyridine (0.949 g, 12 mmol) in dichloromethane (30 mL) was added dropwised a solution of acetic anhydride (1.07 g, 10.5 mmol) at 0°C. The mixture was stirred for 5 hours at room temperature. To the mixture was added water, and then extracted with dichloromethane. The organic layer was dried with Na_2SO_4, and concentrated *in vacuo*. The residue was washed with n-hexane to give 8-amino-5,7-dichloro-2-naphthyl acetate (2.4 g, 89 %).

Next, to the solution of 8-amino-5,7-dichloro-2-naphthyl acetate (2.41 g, 8.93 mmol) and pyridine (0.847 g, 10.7 mmol) in THF (27 mL) was added phenyl chloroformate (1.47 g, 9.38 mmol) at room temperature. The mixture was stirred for 2.5 hours at 50°C. To the reaction mixture was added ethylacetate and washed with water and brine. The organic layer was concentrated *in vacuo*. The residue was washed with n-hexane to give 5,7-dichloro-8-[(phenoxycarbonyl)amino]-2-naphthyl acetate (3.19 g, 92 %).

[Starting compound L]



To a stirred solution of 8-amino-2-naphthol (5.00 g, 31.4 mmol) in a mixture of tetrahydrofuran (50 mL) and dichloromethane (100 mL) was added di-t-butyl-dicarbonate (6.86 g, 31.4 mmol). The mixture was stirred at 70°C for 18 hours. After the mixture was cooled to room temperature, saturated aqueous solution of sodium carbonate was added and the product was extracted with dichloromethane. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (dichloromethane:ethylacetate, 9:1) to afford tert-butyl 7-hydroxy-1-naphthylcarbamate (5.4 g, 66 % yield).

Next, to a mixture of tert-butyl 7-hydroxy-1-naphthylcarbamate (4.67 g, 18.0 mmol) and triethylamine (2.77 g, 27.4 mmol) in dichloromethane (170 mL) was added methanesulfonic anhydride (3.56 g, 19.8 mmol) at 0°C. The mixture was stirred for 30 minutes and poured into saturated aqueous sodium bicarbonate solution. The organic layer was extracted, dried over Na_2SO_4, filtered and concentrated under

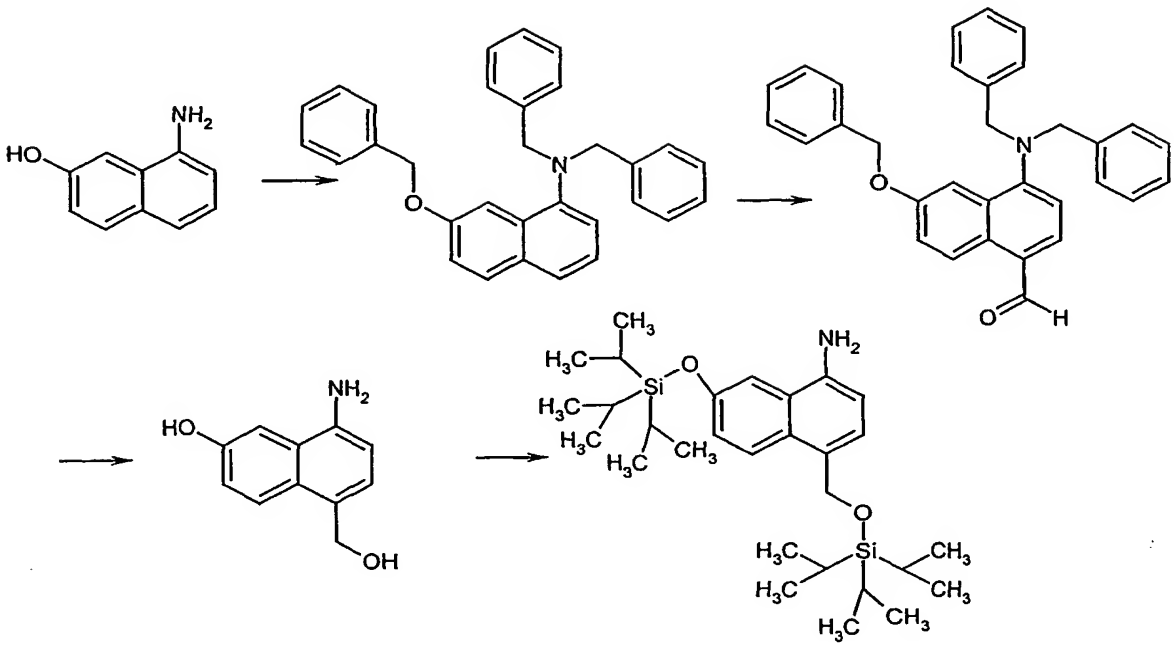
reduced pressure to give 8-[(tert-butoxycarbonyl)amino]-2-naphthyl methanesulfonate (5.8 g, 95 % yield).

Next, to a solution of 8-[(tert-butoxycarbonyl)amino]-2-naphthyl methanesulfonate (2.05 g, 6.08 mmol) in 50 mL acetic acid was added N-bromosuccinimide (1.14 g, 6.41 mmol). The mixture was stirred for 2 hours, and water (100 mL) and dichloromethane (100 mL) were added. The aqueous layer was adjusted to pH 7 by addition of 10 N aqueous sodium hydroxide. The organic layer was extracted, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with a mixture of hexane and ethylacetate to give 5-bromo-8-[(tert-butoxycarbonyl)amino]-2-naphthyl methanesulfonate (1.8 g, 71 % yield).

Next, a mixture of 5-bromo-8-[(tert-butoxycarbonyl)amino]-2-naphthyl methanesulfonate (1.77 g, 4.24 mmol) and 10% aqueous sodium hydroxide solution (85 mL) in tetrahydrofuran (50 mL) was stirred at 50°C for 60 hours. The mixture was cooled to 0°C and neutralized with concentrated hydrochloric acid. The mixture was concentrated under reduced pressure, and the product was extracted with ethylacetate. The organic layer was passed through Celite, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tert-butyl 4-bromo-7-hydroxy-1-naphthylcarbamate (1.3 g, 90 % yield).

Next, a mixture of tert-butyl 4-bromo-7-hydroxy-1-naphthylcarbamate (198 mg, 0.585 mmol) in 4 N HCl in 1,4-dioxane (5 mL) was stirred for 1 hour. The mixture was concentrated under reduced pressure and was added ethylacetate and saturated aqueous sodium bicarbonate solution. The extracted organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 8-amino-5-bromo-2-naphthol (143 mg, 100 % yield).

[Starting compound M]



To a stirred mixture of 8-amino-2-naphthol (24.2 g, 152.0 mmol) and Potassium carbonate in acetone (350 mL) was added benzyl bromide (117.0 g, 684.1 mmol) at 0°C. The mixture was refluxed for 48 hours. After the mixture was cooled to room temperature, the mixture was filtered and the filtrate was concentrated *in vacuo*. To the resulted residue was added diethyl ether, and the precipitates were collected and dried to afford N,N-dibenzyl-7-(benzyloxy)-1-naphthalenamine (50.9 g, 78 % yield).

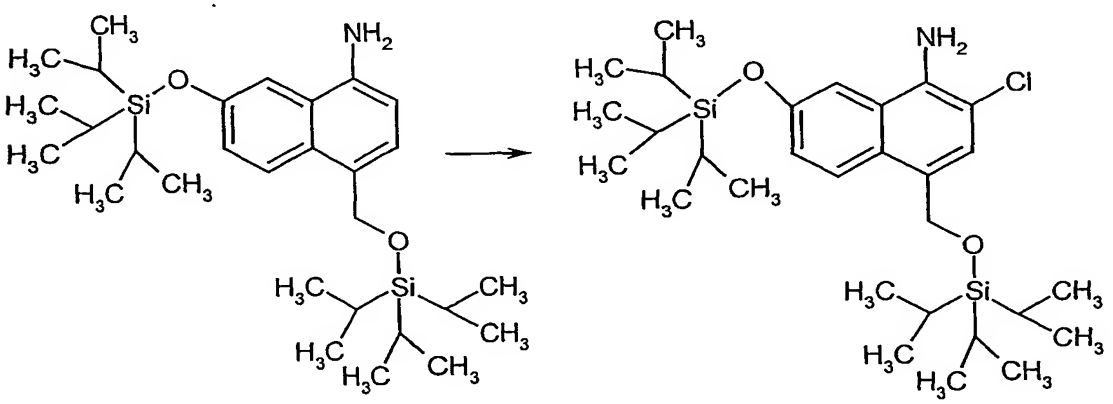
Next, to a stirred solution of N,N-dimethylformamide (100 mL) was added Phosphorus oxychloride (61.2 g, 399.2 mmol) over 30 minutes at 0°C. After stirred for 30 minutes, to the mixture was added N,N-dibenzyl-7-(benzyloxy)-1-naphthalenamine (49.0 g, 114.1 mmol) in N,N-dimethylformamide (400 mL). The mixture was stirred at room temperature for 16 hours, and then poured into ice-water. The product mixture was extracted with dichloromethane, and the organic layer was washed with water, aqueous sodium bicarbonate, and brine. After dried over Na_2SO_4, filtered, and concentrated under reduced pressure, the residue was mixed with ethylacetate and

hexane. The precipitates were collected and dried to give 6-(benzyloxy)-4-(dibenzylamino)-1-naphthaldehyde (45.1 g, 86 % yield).

Next, to a mixture of 6-(benzyloxy)-4-(dibenzylamino)-1-naphthaldehyde (3.00 g, 6.56 mmol) and 10 % Pd/Carbon (0.10 g) in methanol (30 mL) was stirred under hydrogen for 3 days. The mixture was passed through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography (silica gel, 1:1 hexane / ethylacetate) to give 8-amino-5-(hydroxymethyl)-2-naphthol (0.95 g, 76 % yield).

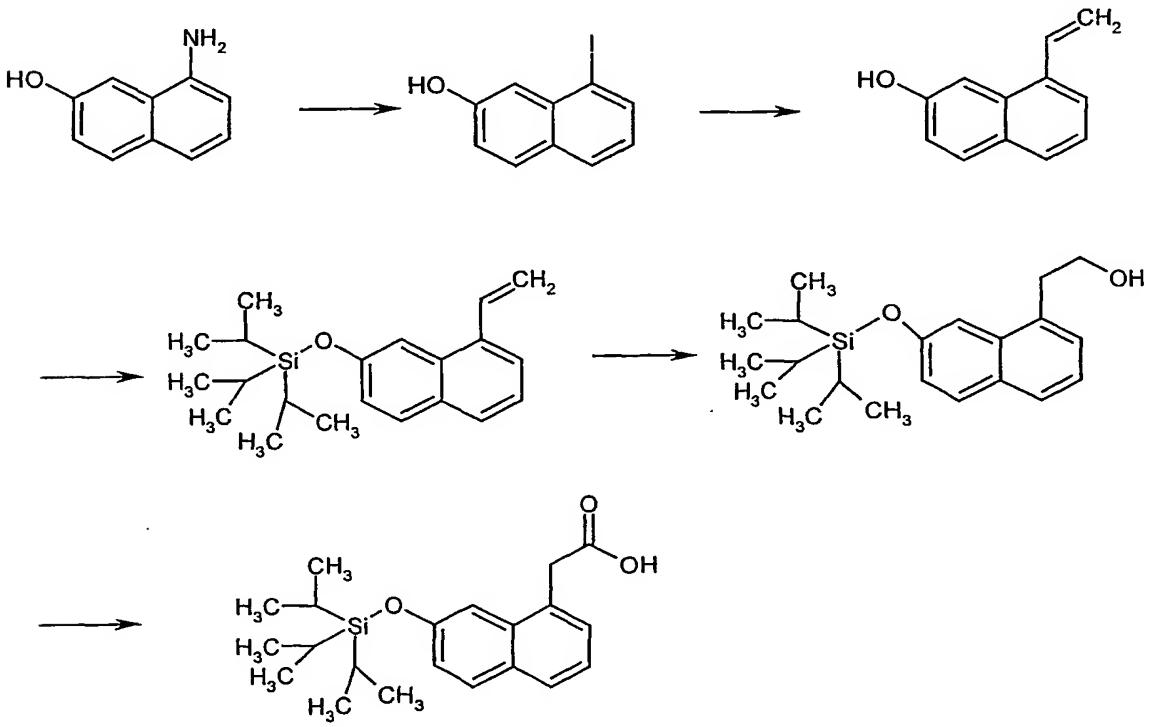
Next, to a mixture of 8-amino-5-(hydroxymethyl)-2-naphthol (0.95 g, 5.02 mmol), imidazole (0.75 g, 11.1 mmol), and 4-dimethylaminopyridine (0.06 g, 0.50 mmol) in N,N-dimethylformamide (10 mL) was added chlorotriisopropylsilane (2.03 g, 10.5 mmol) at 0°C. After the mixture was stirred at room temperature for 16 hours, water was added, and the product was extracted with diethylether. The organic layer was washed with aqueous 10 % citric acid, saturated aqueous sodium bicarbonate, and then with brine. The solvent was removed under reduced pressure, and the obtained residue was purified by column chromatography (silica gel, 10:1 hexane / ethylacetate) to give 7-[(triisopropylsilyl)oxy]-4-{[(triisopropylsilyl)oxy]methyl}-1-naphthylamine (1.67 g, 66 % yield).

[Starting compound N]



To a stirred solution of 7-[(triisopropylsilyl)oxy]-4-{[(triisopropylsilyl)oxy]methyl}-1-naphthylamine (300 mg, 0.60 mmol) in tetrahydrofuran (3.0 mL) was added N-chlorosuccimide (95.8 mg, 0.72 mmol) at 0°C. The mixture was stirred for 2 hours, and then saturated aqueous sodium bicarbonate was added. The mixture was extracted with ethylacetate, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by column chromatography (silica gel, 19:1 hexane / ethylacetate) to give 2-chloro-7-[(triisopropylsilyl)oxy]-4-{[(triisopropylsilyl)oxy]methyl}-1-naphthylamine (112 mg, 35 % yield).

[Starting compound O]



To a mixture of 8-amino-2-naphthol (10.0 g, 62.8 mmol) in tetrahydrofuran (50 mL) and aqueous 3 N hydrochloric acid (100 mL) was added sodium nitrite (4.77 g, 69.1 mmol) in water (15 mL) at 0°C. After stirred for 15 minutes, a solution of

potassium iodide (20.8 g, 125.6 mmol) in water (15 mL) was added, and the mixture was stirred at 0°C for 1 hour. To the reaction mixture was added ethylacetate, and filtered. The filtrate was washed with water, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane: ethylacetate, 4:1) to give 8-iodo-2-naphthol (4.41 g, 26 % yield).

Next, a mixture of 8-iodo-2-naphthol (2.00 g, 7.41 mmol), tributyl(vinyl)tin (2.82 g, 8.89 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.171 g, 0.148 mmol) in toluene (15 mL) was stirred at 90°C for 16 hours. The mixture was poured into water and extracted with ethylacetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethylacetate, 10:1) to give 8-vinyl-2-naphthol (1.26 g, 100 % yield).

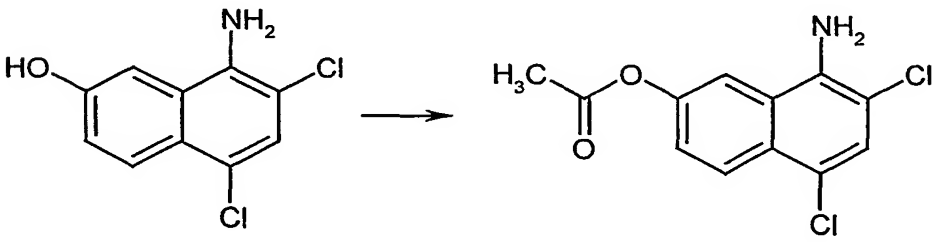
Next, to a solution of 8-vinyl-2-naphthol (1.38 g, 8.10 mmol) and imidazole (0.827 g, 12.1 mmol) in N,N-dimethylformamide (10 mL) was added chlorotriisopropylsilane (1.87 g, 9.72 mmol) at room temperature. The mixture was stirred at 50°C for 16 hours and was poured into water and extracted with ethylacetate. The organic layer dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane) to give triisopropyl-[(8-vinyl-2-naphthyl)oxy]silane (1.65 g, 63 % yield).

Next, to a solution of triisopropyl-[(8-vinyl-2-naphthyl)oxy]silane (0.500 g, 1.53 mmol) in tetrahydrofuran (3 mL) was added 0.5 M 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (3.0 mL) at 0°C. The mixture was stirred at room temperature for 5 hours, then 3 N aqueous sodium hydroxide (3.0 mL) and 35 % aqueous hydrogen peroxide (3.0 mL) were added, and stirred at room temperature for 16 hours. To the mixture was added ethylacetate, and the extracted organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography

(hexane:ethylacetate, 10:1) to give 2-{7-[(triisopropylsilyl)oxy]-1-naphthyl}ethanol (0.296 g, 56 % yield).

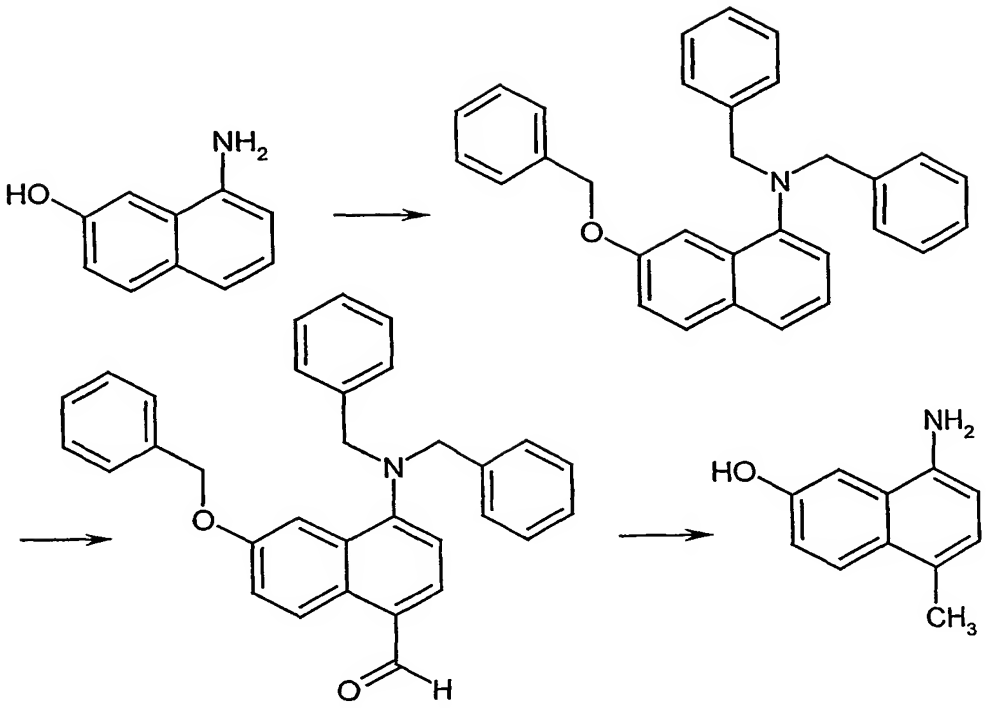
Next, a stock solution of periodic acid (11.4 g, 50.0 mmol) and chromium(VI)oxide (23.0 mg) in 114 mL of acetonitrile (0.75 volume % water) was prepared. To a solution of 2-{7-[(triisopropylsilyl)oxy]-1-naphthyl}ethanol (59.0 mg, 0.171 mmol) in acetonitrile (1 mL) was added the periodic acid / chromium(VI)oxide stock solution (1.0 mL) at 0°C. After stirred for 30 minutes, aqueous solution of sodium hydrogenphosphate (60.0 mg, in 1.0 mL water) and toluene (1.5 mL) were added. The organic layer was separated and washed with brine and aqueous sodium hydrogensulfate, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethylacetate, 4:1) to give {7-[(triisopropylsilyl)oxy]-1-naphthyl}acetic acid (15.0 mg, 24 % yield).

[Starting compound P]



To a solution of 8-amino-5,7-dichloro-2-naphthol (2.28 g, 10.0 mmol) and pyridine (0.949 g, 12 mmol) in dichloromethane (30 mL) was added dropwised a solution of acetic anhydride (1.07 g, 10.5 mmol) at 0 °C. The mixture was stirred for 5 hours at room temperature. To the mixture was added water, and then extracted with dichloromethane. The organic layer was dried with Na_2SO_4, and concentrated *in vacuo*. The residue was washed with n-hexane to give 8-amino-5,7-dichloro-2-naphthyl acetate (2.4 g, 89 %).

[Starting compound Q]



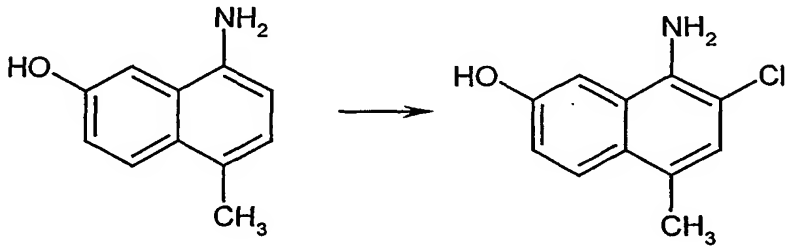
To a stirred mixture of 8-amino-2-naphthol (24.2 g, 152.0 mmol) and Potassium carbonate in acetone (350 mL) was added benzyl bromide (117.0 g, 684.1 mmol) at 0°C. The mixture was refluxed for 48 hours. After the mixture was cooled to room temperature, the mixture was filtered and the filtrate was concentrated *in vacuo*. To the resulted residue was added diethyl ether, and the precipitates were collected and dried to afford N,N-dibenzyl-7-(benzyloxy)-1-naphthalenamine (50.9 g, 78 % yield).

Next, to a stirred solution of N,N-dimethylformamide (100 mL) was added Phosphorus oxychloride (61.2 g, 399.2 mmol) over 30 minutes at 0°C. After stirred for 30 minutes, to the mixture was added N,N-dibenzyl-7-(benzyloxy)-1-naphthalenamine (49.0 g, 114.1 mmol) in N,N-dimethylformamide (400 mL). The mixture was stirred at room temperature for 16 hours, and then poured into ice-water. The product mixture was extracted with dichloromethane, and the organic layer was washed with water, aqueous sodium bicarbonate, and brine. After dried over Na_2SO_4, filtered, and concentrated under reduced pressure, the residue was mixed with ethylacetate and

hexane. The precipitates were collected and dried to give 6-(benzyloxy)-4-(dibenzyl-amino)-1-naphthaldehyde (45.1 g, 86 % yield).

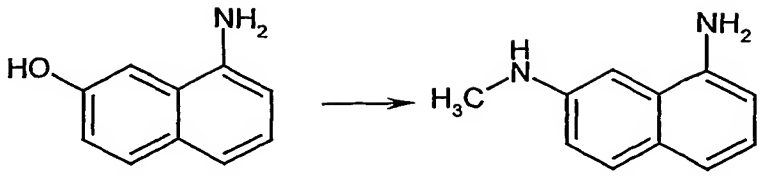
Next, to a mixture of 6-(benzyloxy)-4-(dibenzylamino)-1-naphthaldehyde (200.7 mg, 0.439 mmol) and 10 % Pd/Carbon (54.0 mg) in methanol (10 mL) was stirred under high pressure hydrogen for 2 days. The mixture was passed through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography (silica gel, 1:1 hexane / ethylacetate) to give 8-amino-5-methyl-2-naphthol (173.2 mg, 88 % yield).

[Starting compound R]



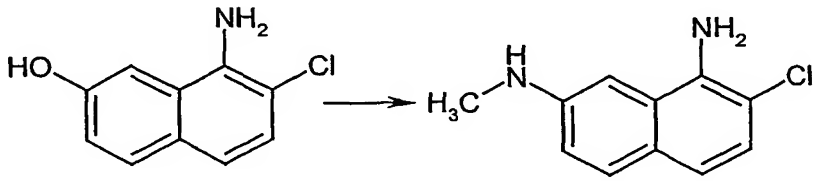
To a stirred solution of 8-amino-5-methyl-2-naphthol (150.0 mg, 0.87 mmol) in tetrahydrofuran (10 mL) was added N-chlorosuccinimide (115.6 mg, 0.87 mmol) at 0°C. The reaction mixture was stirred for 5 hours at room temperature, and the mixture was concentrated under reduced pressure. Ethylacetate was added to the mixture, and the organic layer was washed with water, dried over MgSO4, filtered, and concentrated under reduced pressure. The obtained residue was triturated with dichloromethane and diisopropylether, filtered, and the filtrate was concentrated under reduced pressure to give 8-amino-7-chloro-5-methyl-2-naphthol (157.0 mg, 87 %).

[Starting compound S]



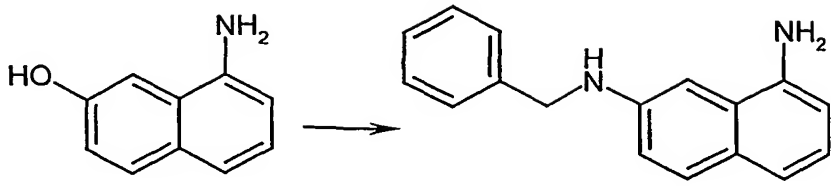
A stirred mixture of 8-amino-2-naphthol (1.00 g, 6.32 mmol) and 40 % methylamine in water (10 mL) was stirred at 160°C in a sealed tube for 2 days. After cooling to room temperature, the mixture was poured into water, and extracted with ethylacetate. The organic layer was washed with water, dried over MgSO4, filtered, and concentrated under reduced pressure. The obtained residue was purified by column chromatography (silica gel, 1:3 hexane / ethylacetate) to give N-(8-amino-2-naphthyl)-N-methylamine (0.478 g, 44 % yield).

[Starting compound T]



A stirred mixture of 8-amino-7-chloro-2-naphthol (195.0 mg, 1.01 mmol) and 40 % methylamine in water (10 mL) was stirred at 180°C in a sealed tube for 24 hours. After cooling to room temperature, the mixture was poured into water, and extracted with ethylacetate. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give N-(8-amino-7-chloro-2-naphthyl)-N-methylamine (16.1 mg, 7.7 % yield).

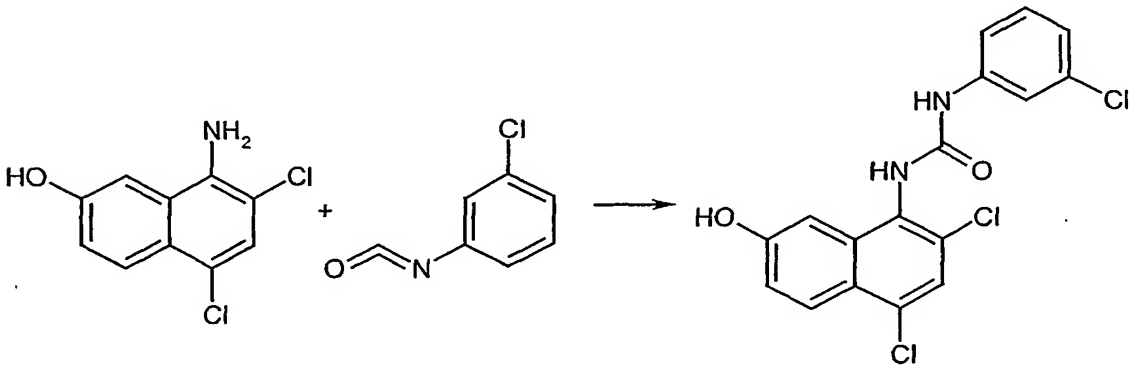
[Starting compound U]



A stirred mixture of 8-amino-2-naphthol (1.10 g, 6.91 mmol) and benzylamine (1.61 g, 15.0 mmol) was stirred at 180 °C in a sealed tube for 2 days. After cooling to room temperature, the mixture was purified by column chromatography (silica gel, 1:2 hexane / ethylacetate) to give N-(8-amino-2-naphthyl)-N-benzylamine (1.39 g, 81 % yield).

Example 1-1

N-(3-Chlorophenyl)-N'-(2,4-dichloro-7-hydroxy-1-naphthyl)urea



This example was performed according to the general method A.

A mixture of 8-amino-5,7-dichloro-2-naphthol (starting compound G) (100 mg, 0.438 mmol) and 3-chlorophenyl isocyanate (67.0 mg, 0.438 mmol) in 1,4-dioxane (5 mL) was stirred at 50°C for 16 hours. The mixture was concentrated under

reduced pressure, and to the residue was added isopropylether. The precipitate was filtered and dried to give N-(3-chlorophenyl)-N'-(2,4-dichloro-7-hydroxy-1-naphthyl)urea (65 mg, 39 % yield).

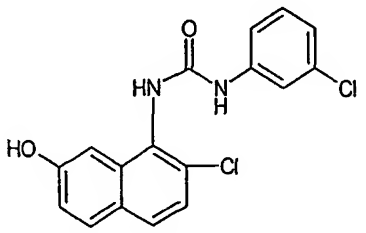
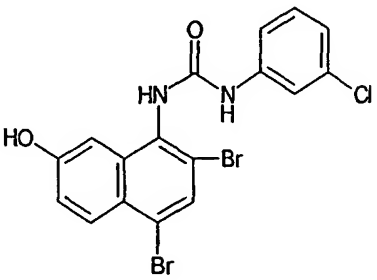
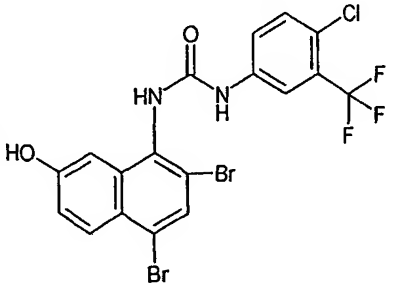
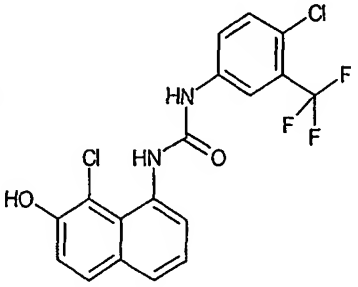
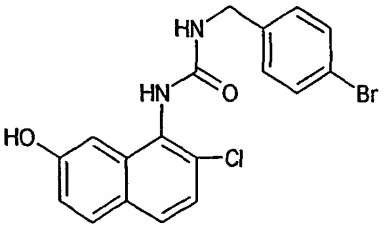
Molecular weight 381.64

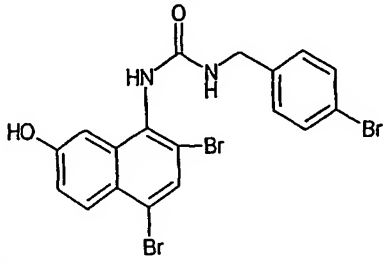
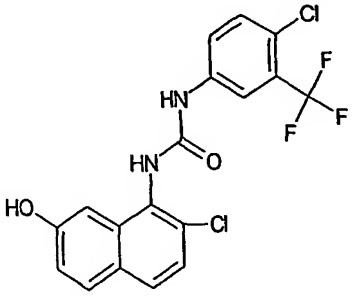
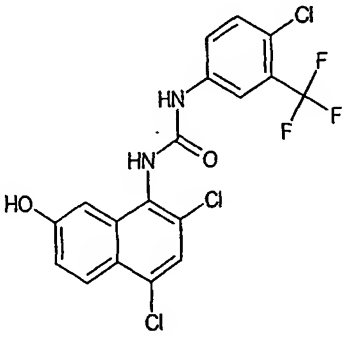
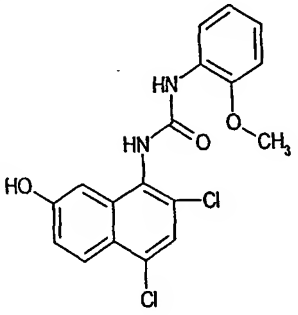
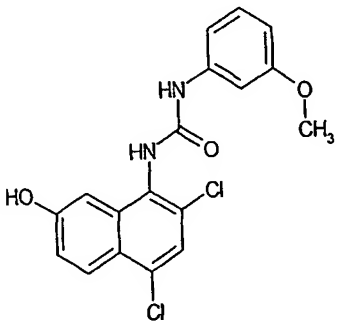
MS (M+H):381

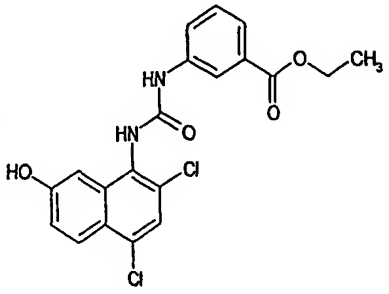
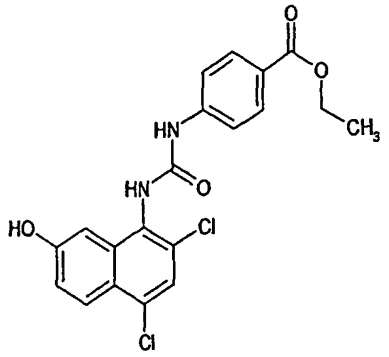
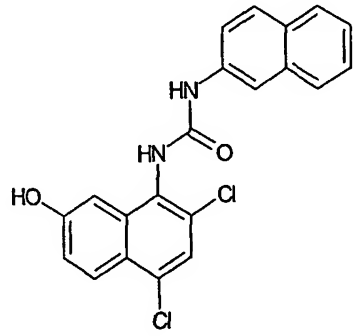
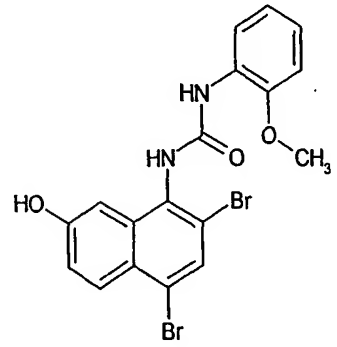
mp:> 260°C

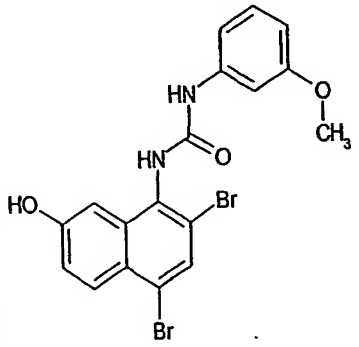
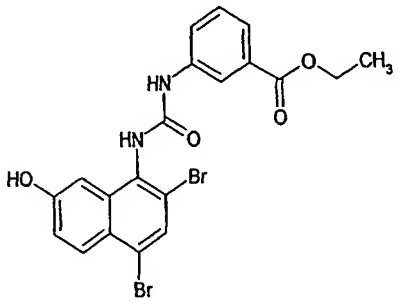
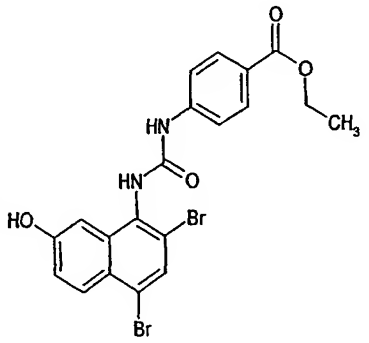
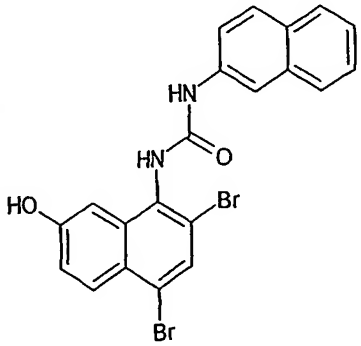
With the use of any of the starting materials A-J , M-N, or Q-U and according to the similar procedure of Example 1-1, the following compounds were synthesized and tested. In the tables, Z stands for decomposition.

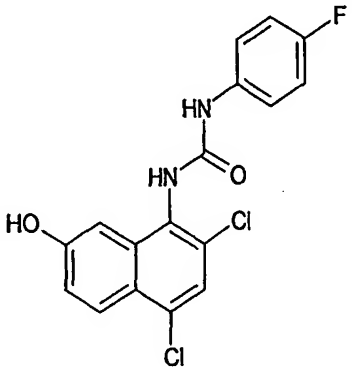
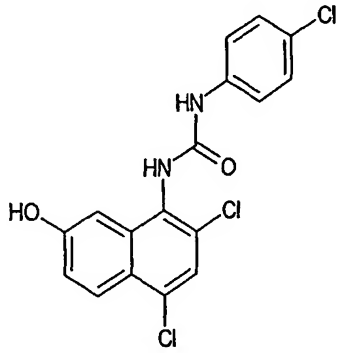
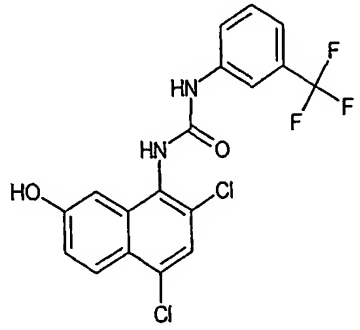
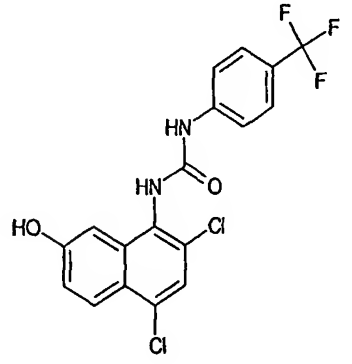
Table 1

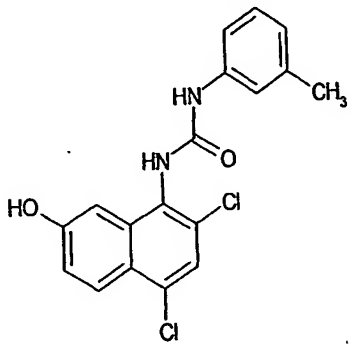
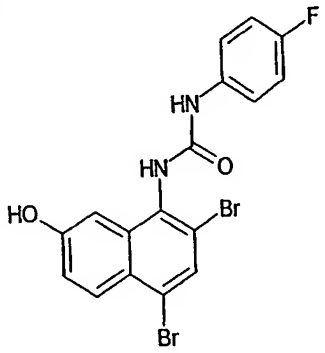
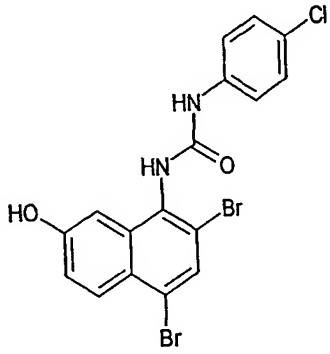
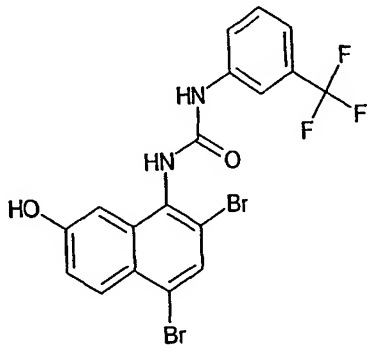
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-2		347,2034	347	242-243
1-3		470,5504	470	242-243
1-4		538,5488	536	242-243
1-5		415,2018	416	>240Z
1-6		405,6815	405, 407	226-229

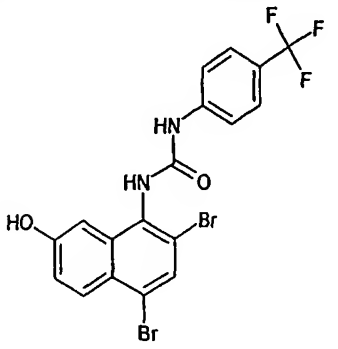
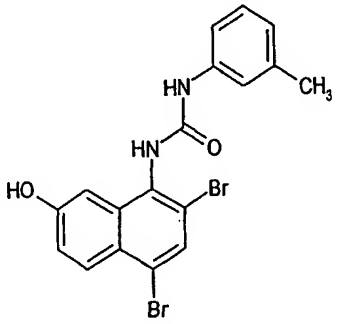
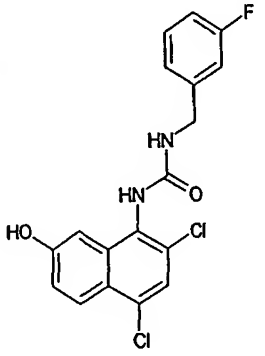
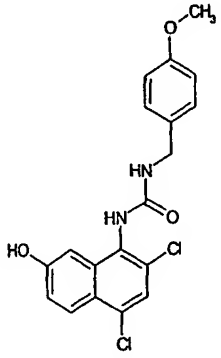
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-7		529,0285		215Z
1-8		415,2018	415	260-Z
1-9		449,6468	449	255-Z
1-10		377,2299	377, 379	251Z
1-11		377,2299	377	223-226

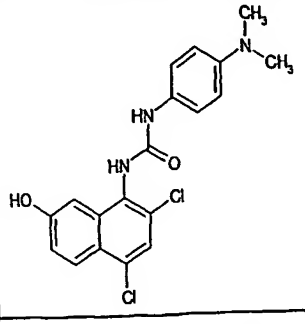
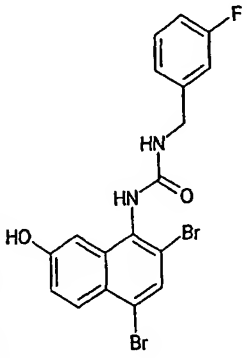
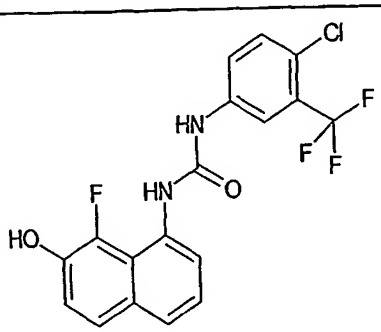
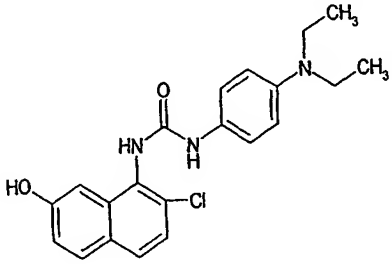
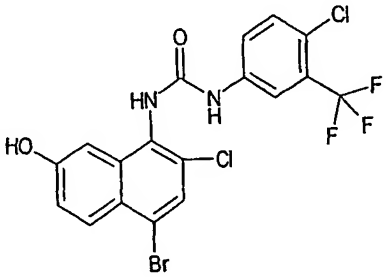
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-12		419,2675	419	234-236
1-13		419,2675	419, 421	258-260
1-14		397,2639	397, 399	263-265
1-15		466,1319	467, 469	228-230

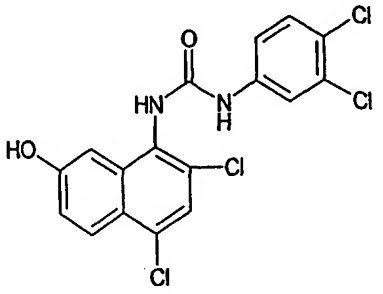
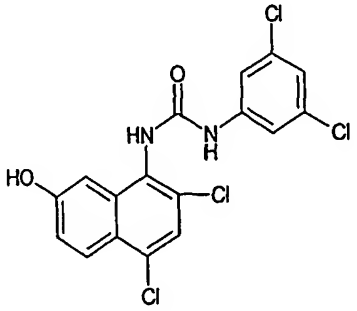
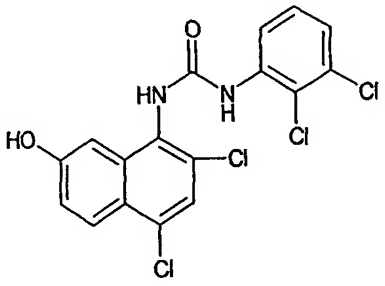
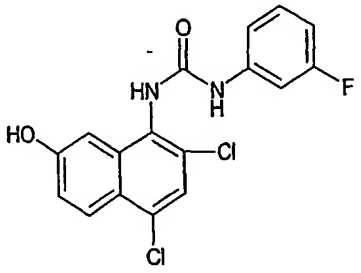
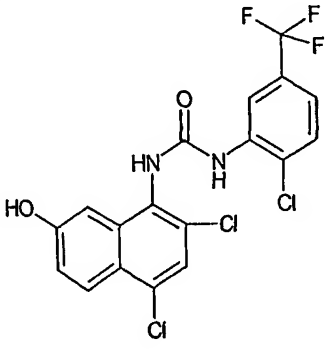
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-16		466,1319	465, 467, 469	213-216
1-17		508,1695	509	193-196
1-18		508,1695	507, 509, 511	209Z
1-19		486,1659	nd	195Z

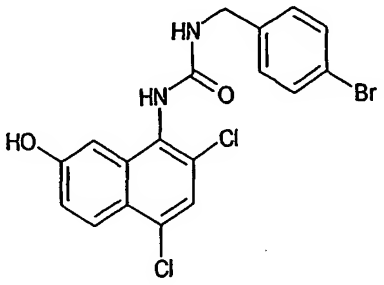
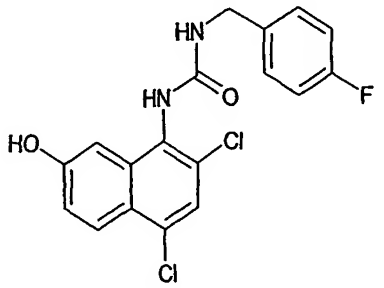
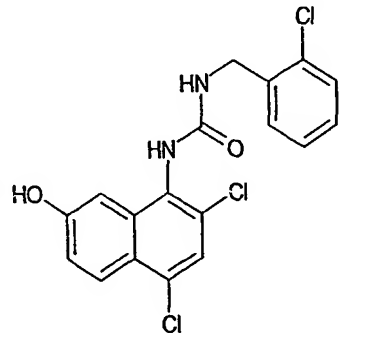
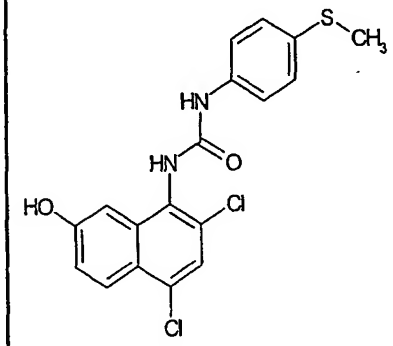
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-20		365,1938	365, 367	250Z
1-21		381,6484	381, 383	253-255
1-22		415,2018	415	262Z
1-23		415,2018	415, 417	268-271

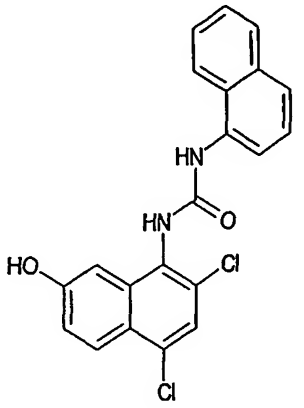
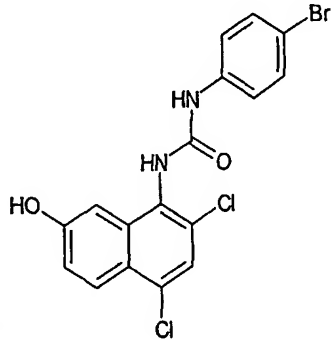
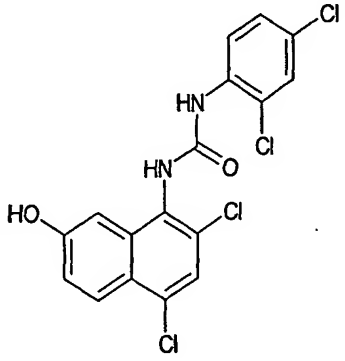
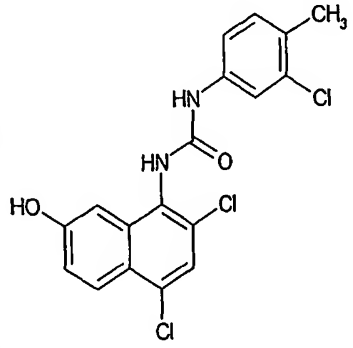
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-24		361,2305	361, 363	223Z
1-25		454,0958	453, 455, 457	222-225
1-26		470,5504	469, 471, 473	229-233
1-27		504,1038	503, 505, 507	233-236

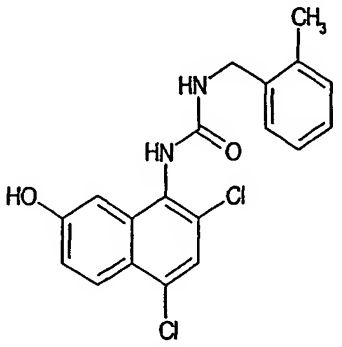
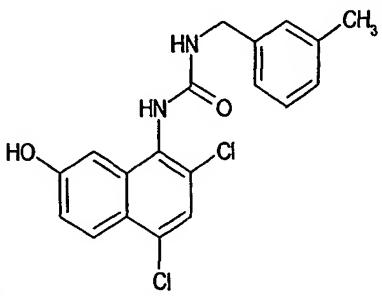
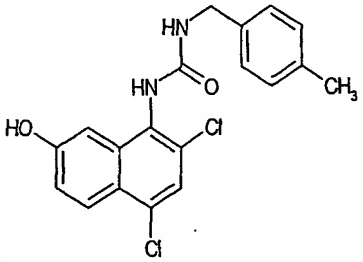
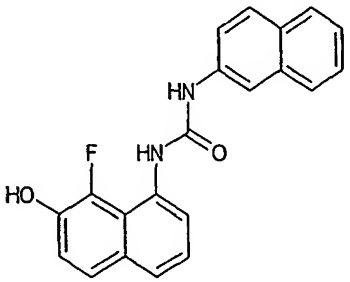
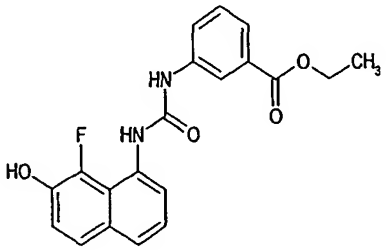
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-28		504,1038	503, 505, 507	229Z
1-29		450,1325	451	164Z
1-30		379,2209	379, 381	225-228
1-31		391,257	391	223-226

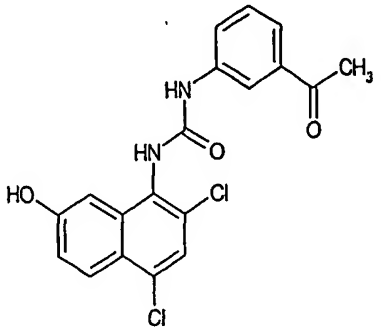
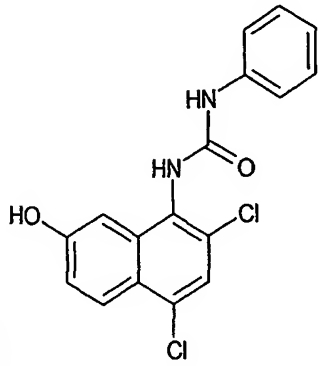
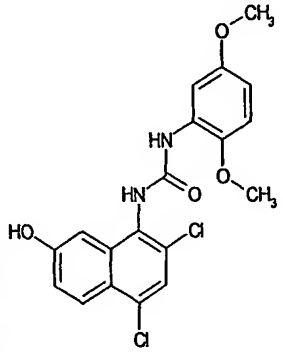
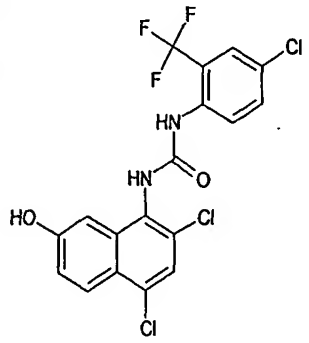
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-32		390,2722	390	192-Z
1-33		468,1229	467, 469, 471	215-218
1-34		398,7472	399	228
1-35		383,8814		199.8-200.5
1-36		494,0978		209Z

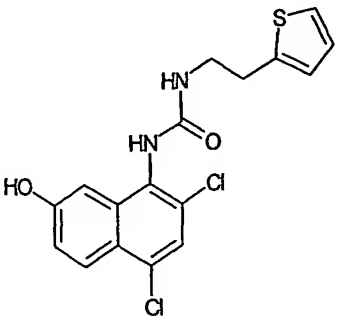
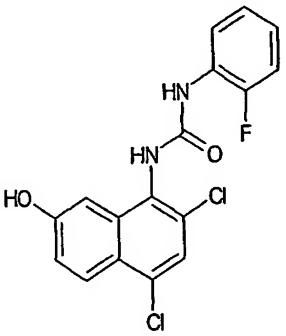
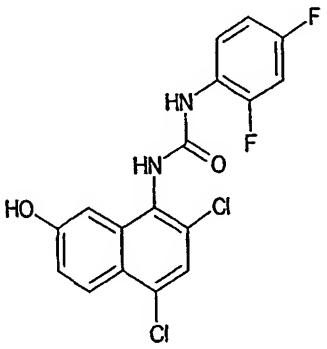
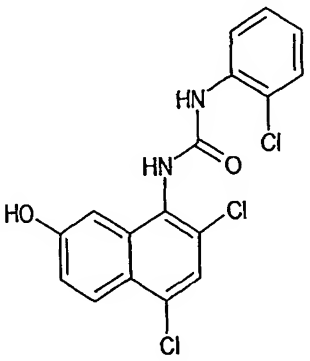
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-37		416,0935	415	249 Z
1-38		416,0935	415	265 Z
1-39		416,0935	415	300
1-40		365,1938	365	>300
1-41		449,6468	449	>300

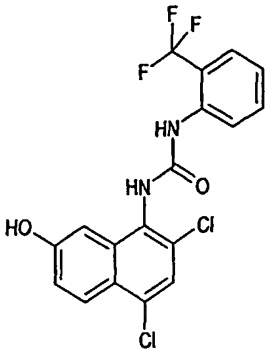
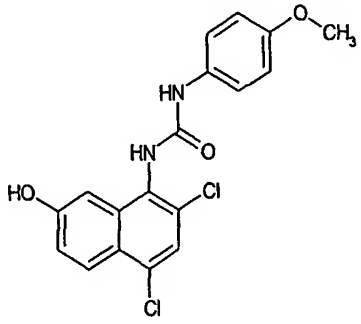
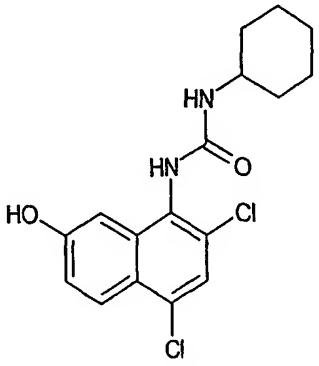
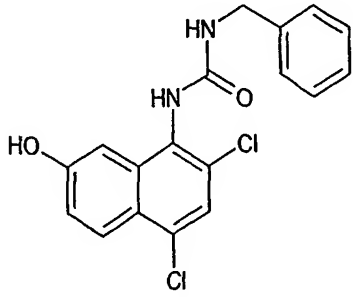
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-42		440,1265	439	226 Z
1-43		379,2209	379	229 Z
1-44		395,6755	395	240 Z
1-45		393,2945	393	>231 Z

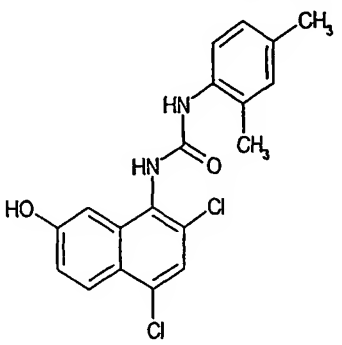
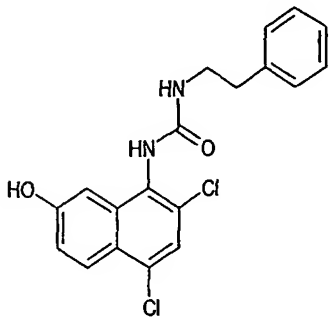
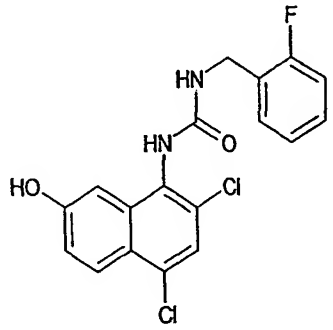
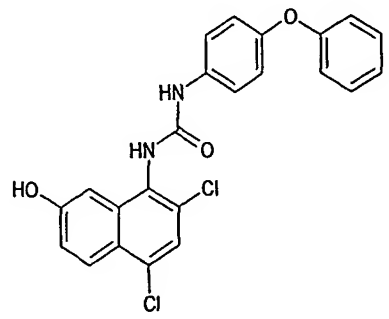
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-46		397,2639	397	269 Z
1-47		426,0994	424	258 Z
1-48		416,0935	nd	286 Z
1-49		395,6755	395	248 Z

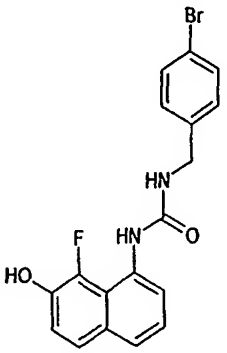
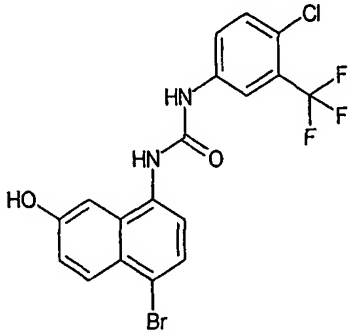
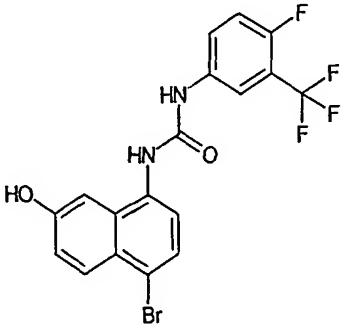
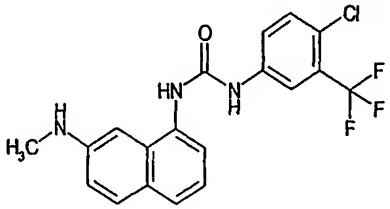
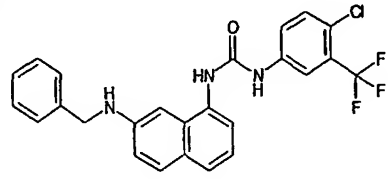
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-50		375,2576	375	239 Z
1-51		375,2576	375	227 Z
1-52		375,2576	375	224 Z
1-53		346,3643	347	189
1-54		368,3679	370	174

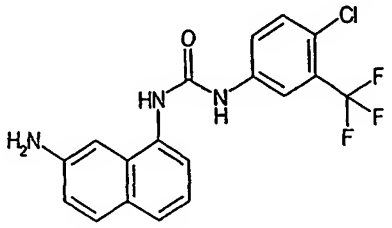
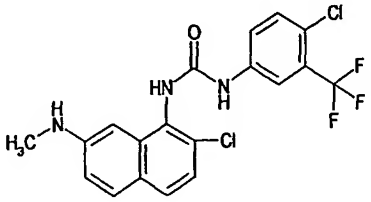
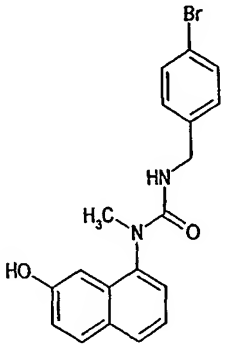
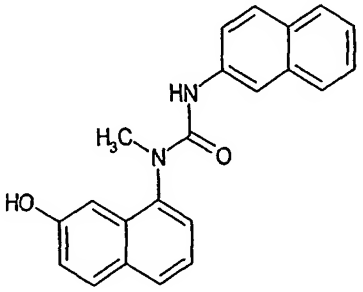
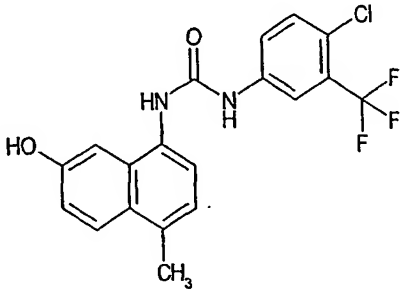
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-55		389,241	389	223 Z
1-56		347,2034	347	245 Z
1-57		407,2564	407	258 Z
1-58		449,6468	449	283 Z

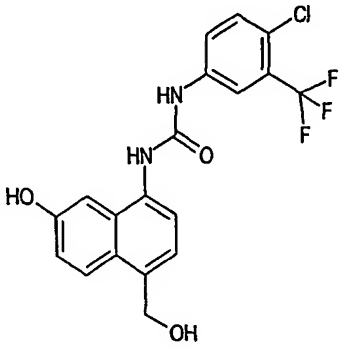
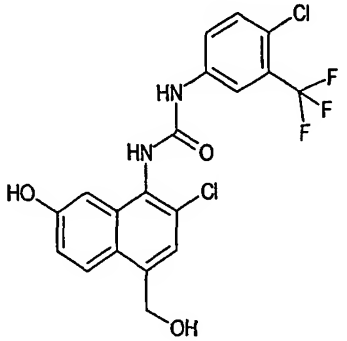
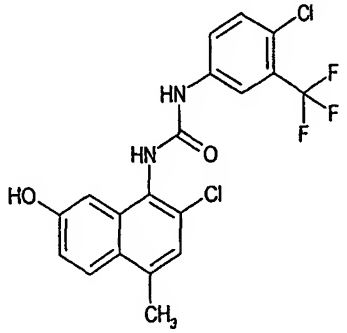
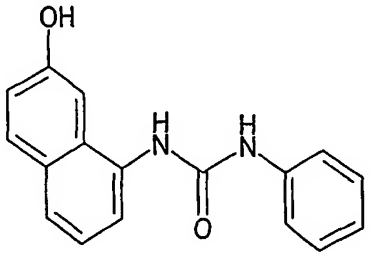
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-59		381,2833	381	234 Z
1-60		365,1938	365	297 Z
1-61		383,1843	383	300 Z
1-62		381,6484	381	250 Z

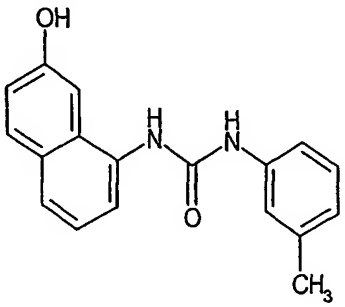
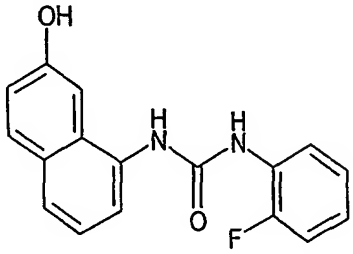
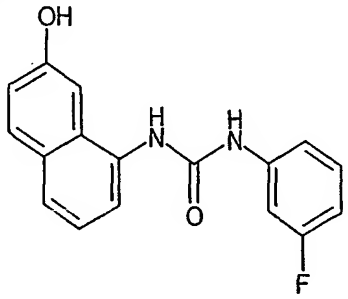
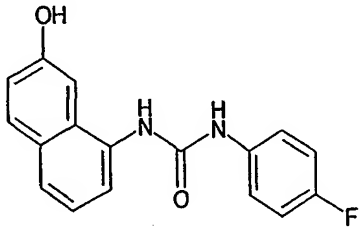
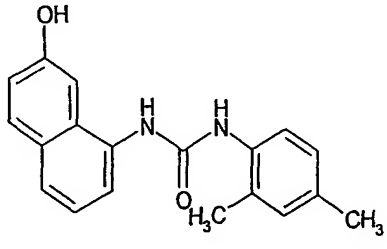
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-63		415,2018	415	300 Z
1-64		377,2299	377	243 Z
1-65		353,2512	353	217 Z
1-66		361,2305	361	220 Z

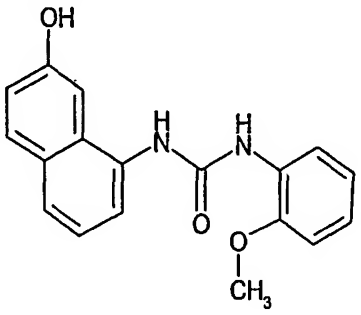
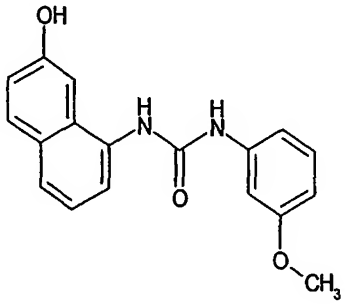
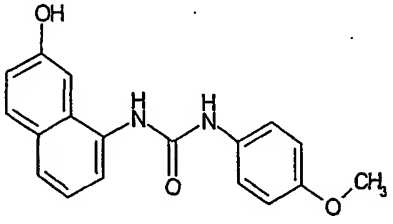
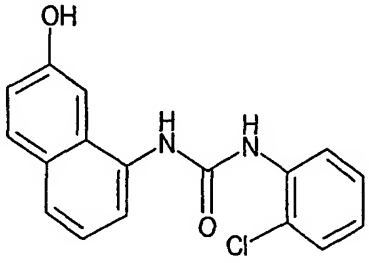
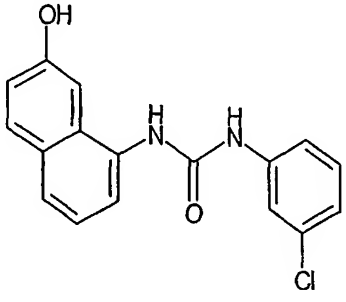
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-67		375,2576	375	254 Z
1-68		375,2576	375	235 Z
1-69		379,2209	379	218 Z
1-70		439,3016	439	230 Z

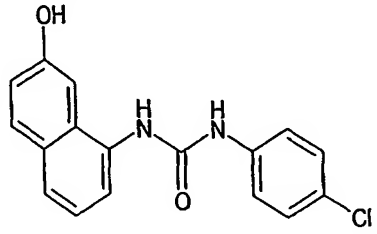
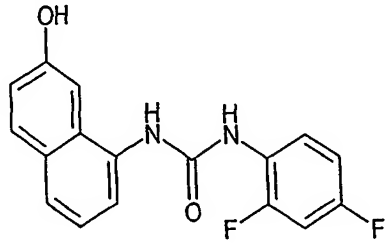
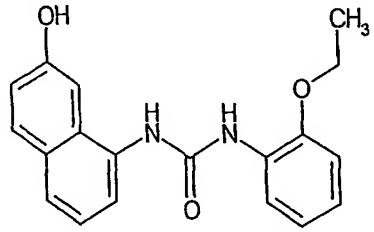
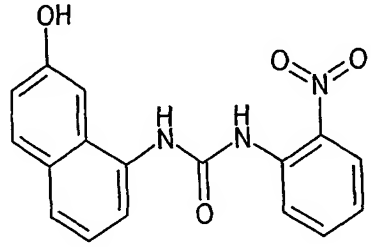
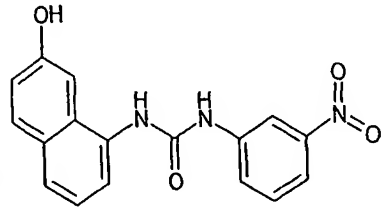
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-71		389,2269	390	210
1-72		459,6528	-	211
1-73		443,1982		215
1-74		393,7991	394	218-219
1-75		469,8979	470	193-194

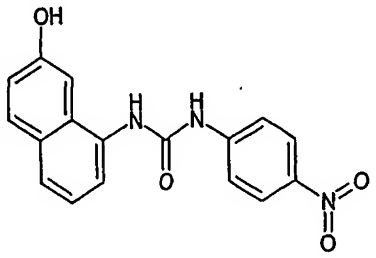
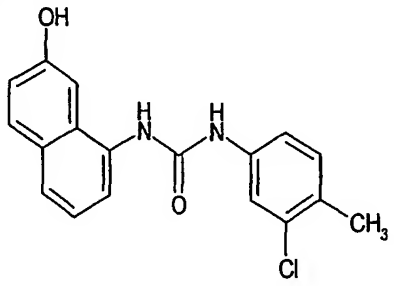
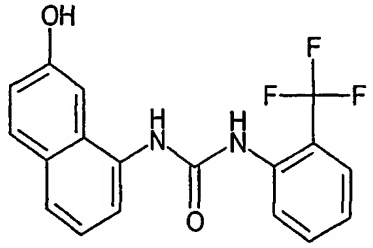
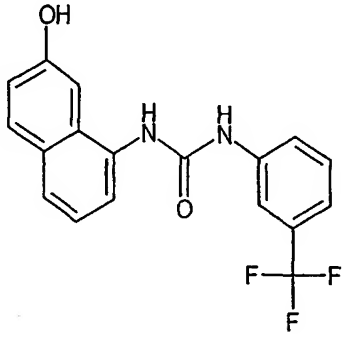
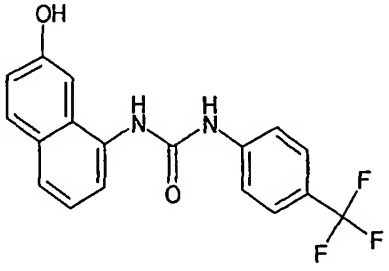
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-76		379,772	380	232-234
1-77		428,2441	429	258-259
1-78		385,2635	386	194
1-79		342,401	343	215
1-80		394,7838	395	237-238

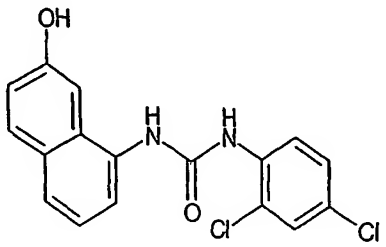
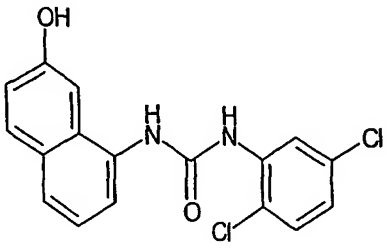
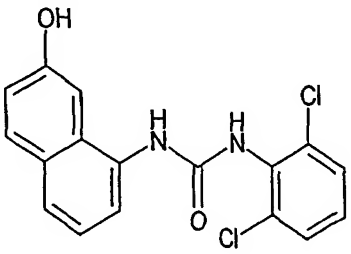
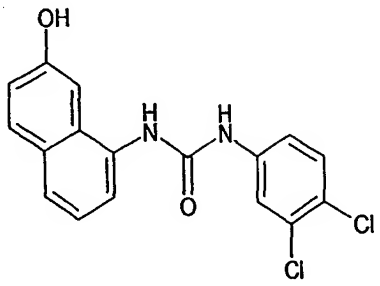
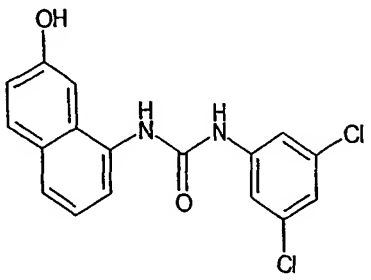
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-81		410,7832	411	201 Z
1-82		445,2283	446	210
1-83		429,2289	430	254
1-84		278,3133	279	

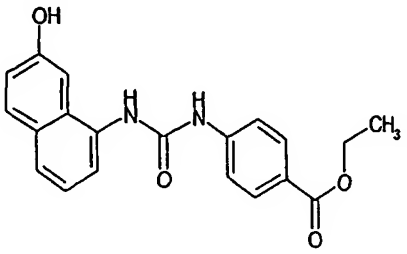
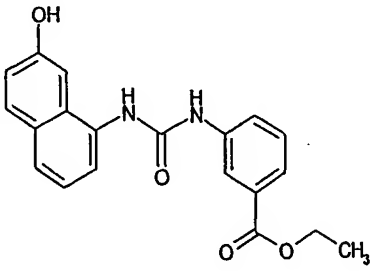
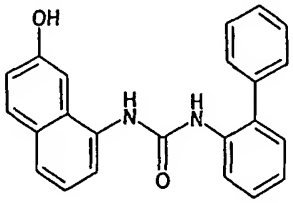
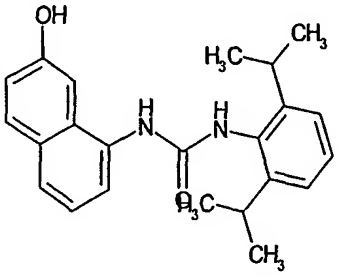
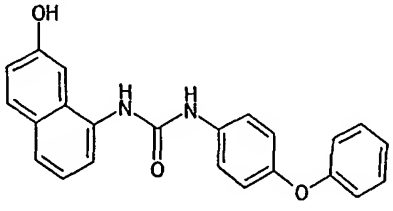
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-85		292,3404	293	
1-86		296,3038	297	
1-87		296,3038	297	
1-88		296,3038	297	
1-89		306,3675	307	

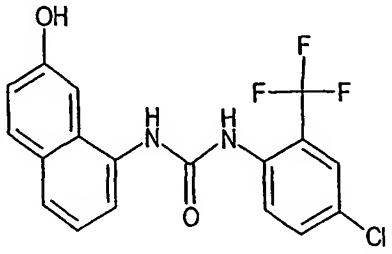
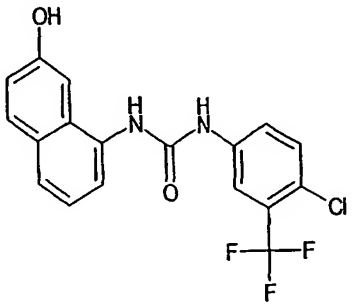
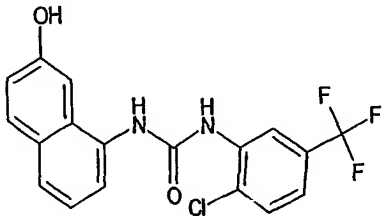
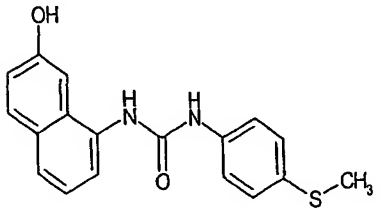
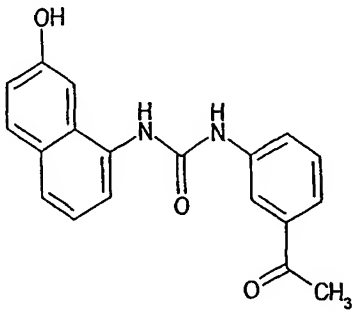
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-90		308,3398	309	
1-91		308,3398	309	
1-92		308,3398	309	
1-93		312,7584	313	
1-94		312,7584	313	

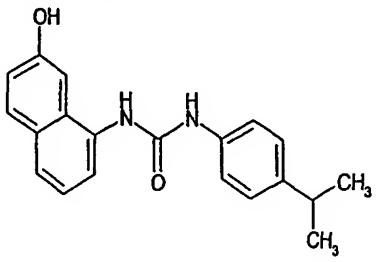
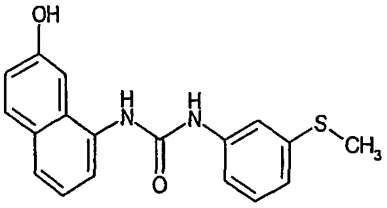
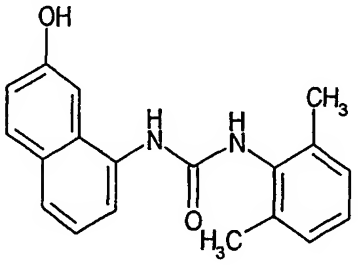
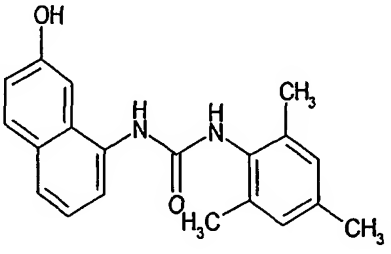
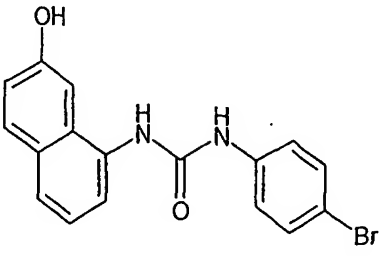
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-95		312,7584	313	
1-96		314,2942	315	
1-97		322,3669	323	
1-98		323,3109	324	
1-99		323,3109	324	

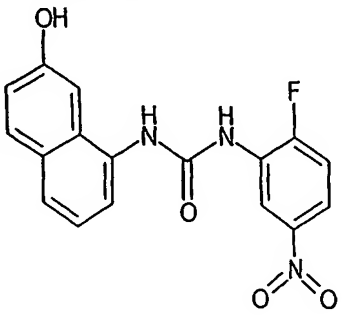
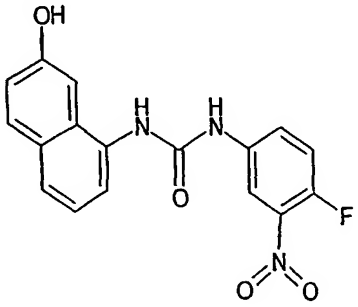
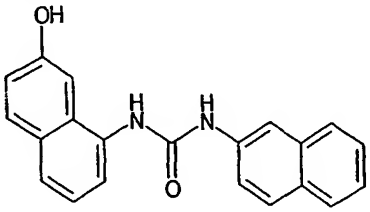
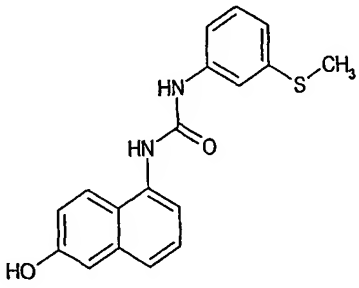
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-100		323,3109	324	
1-101		326,7855	327	
1-102		346,3117	347	
1-103		346,3117	347	
1-104		346,3117	347	

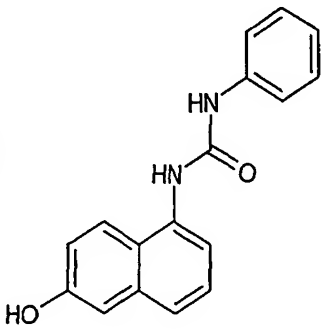
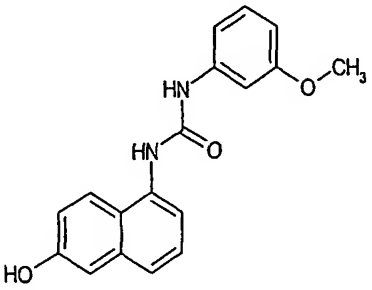
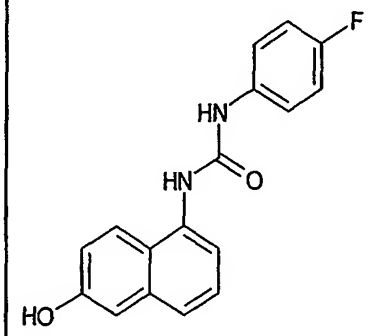
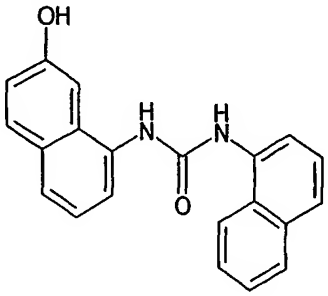
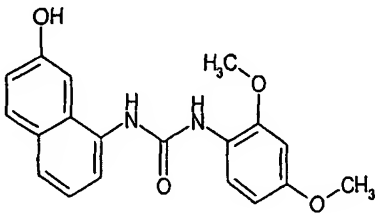
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-105		347,2034	348	
1-106		347,2034	348	
1-107		347,2034	348	
1-108		347,2034	348	
1-109		347,2034	348	

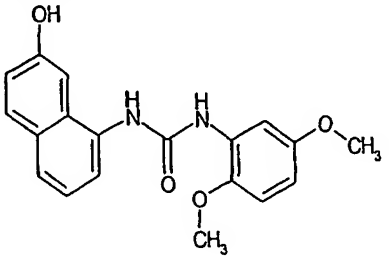
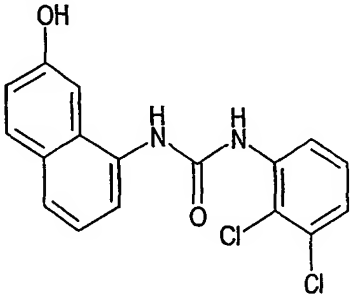
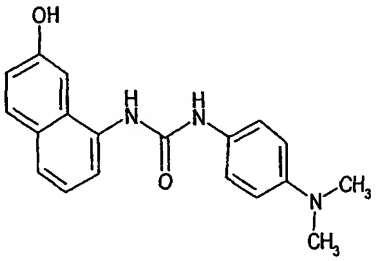
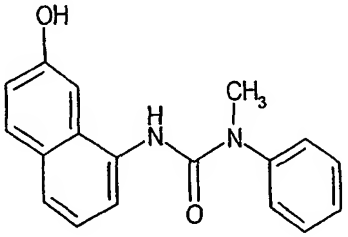
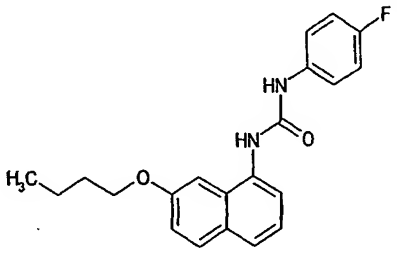
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-110		350,3775	351	
1-111		350,3775	351	
1-112		354,4121	355	
1-113		362,4759	363	
1-114		370,4115	371	

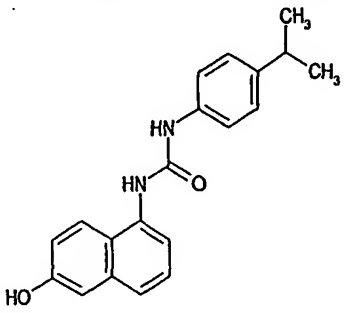
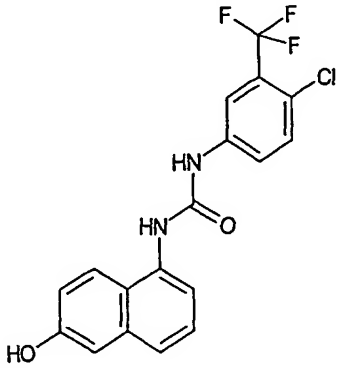
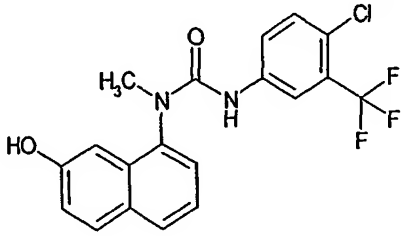
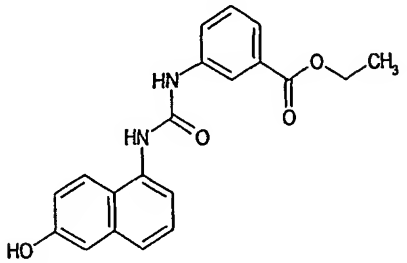
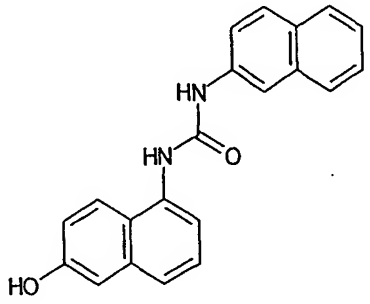
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-115		380,7567	381	
1-116		380,7567	381	
1-117		380,7567	381	
1-118		324,4044	325	
1-119		320,351	321	

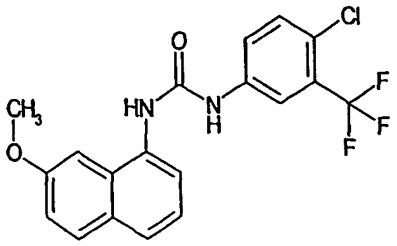
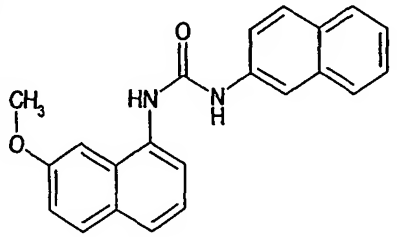
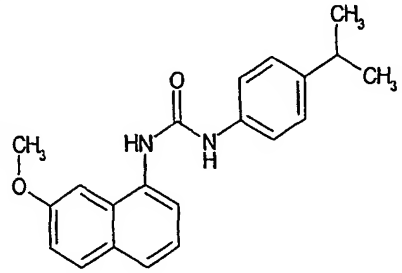
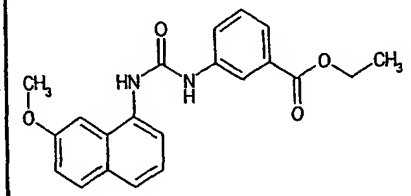
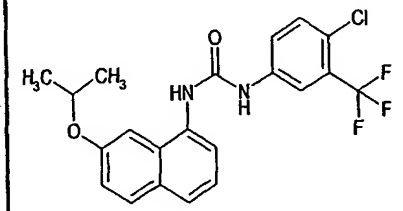
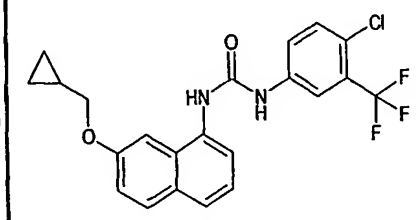
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-120		320,3946	321	
1-121		324,4044	325	
1-122		306,3675	307	
1-123		320,3946	321	
1-124		357,2094	358	

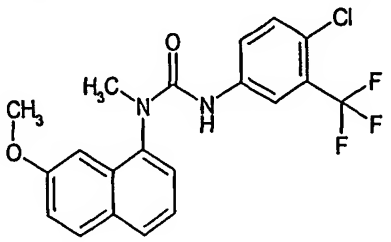
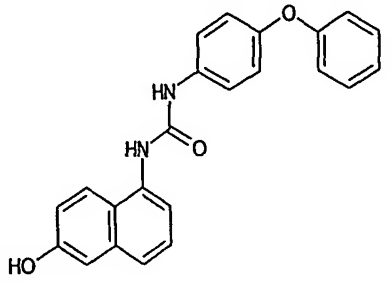
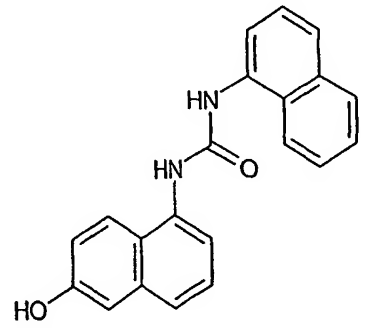
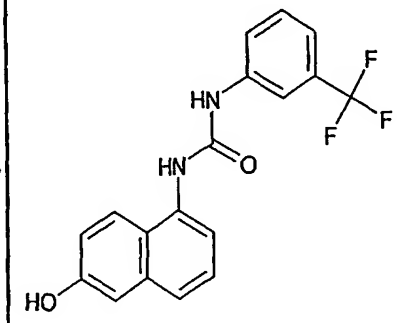
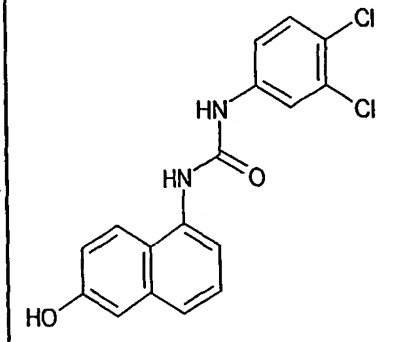
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-125		341,3013	342	
1-126		341,3013	342	
1-127		328,3739	329	
1-128		324,4044	nd	

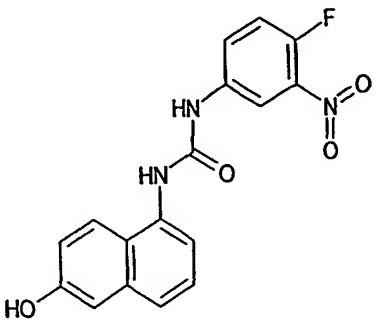
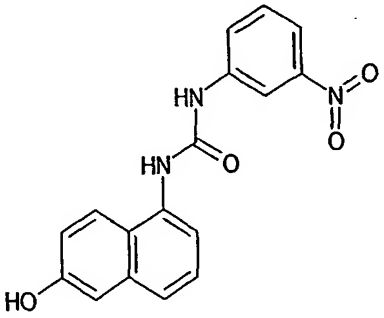
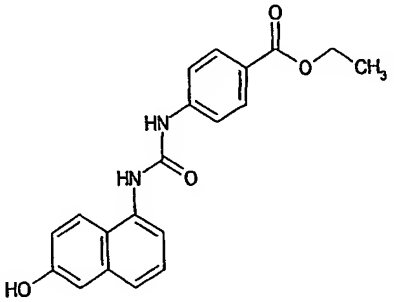
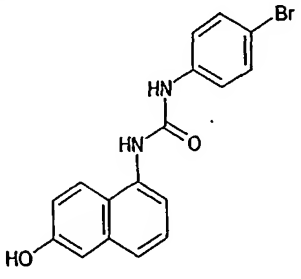
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-129		278,3133	279	
1-130		308,3398	309	
1-131		296,3038	nd	
1-132		328,3739	329	
1-133		338,3663	339	

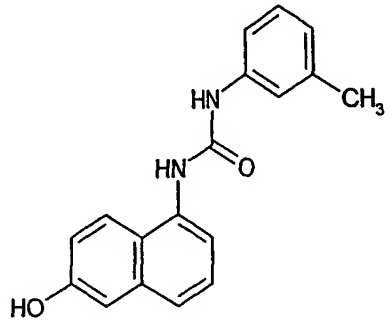
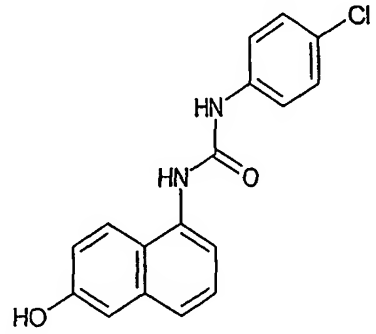
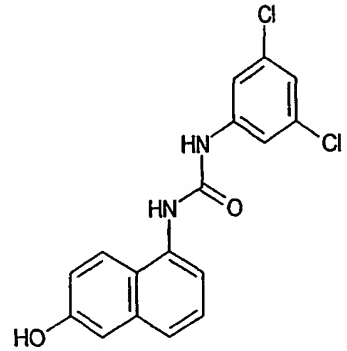
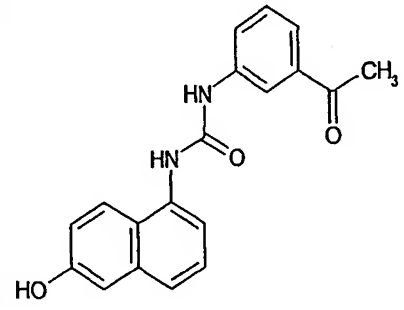
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-134		338,3663	339	
1-135		347,2034	348	
1-136		321,3822	322	
1-137		292,3404	293	
1-138		352,4121	353	

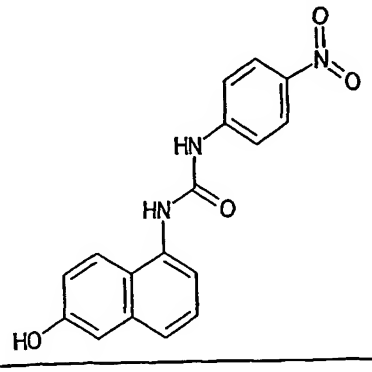
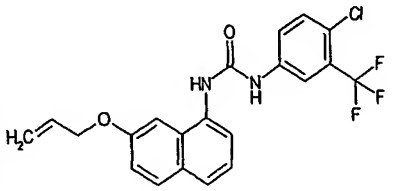
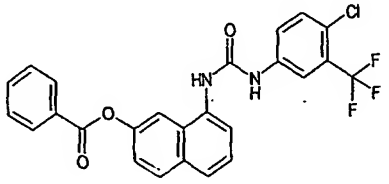
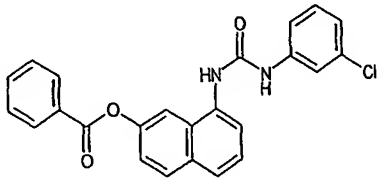
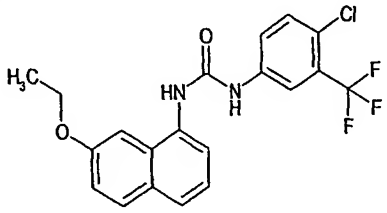
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-139		320,3946	321	207.5
1-140		380,7567	381	
1-141		394,7838	395	
1-142		350,3775	351	
1-143		328,3739	329	

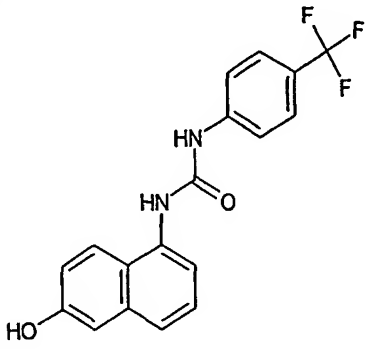
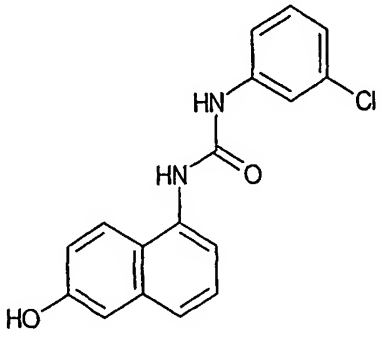
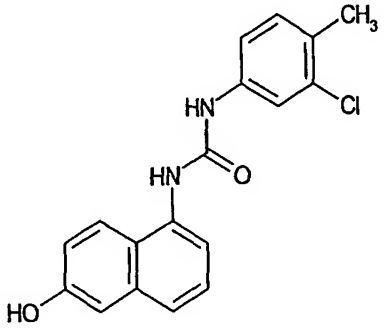
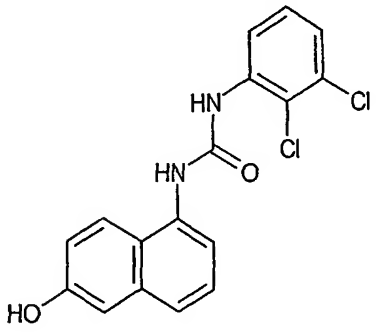
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-144		394,7838	395	
1-145		342,401	343	
1-146		334,4217	335	
1-147		364,4046	365	
1-148		422,838	423	
1-149		434,8492	435	

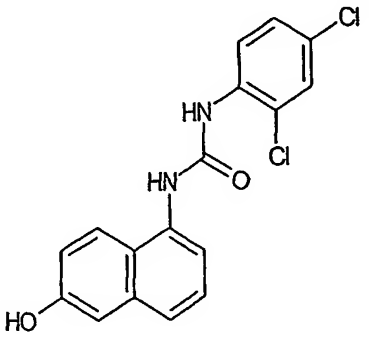
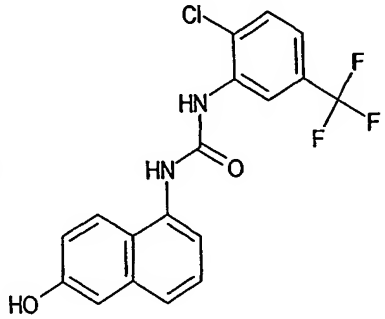
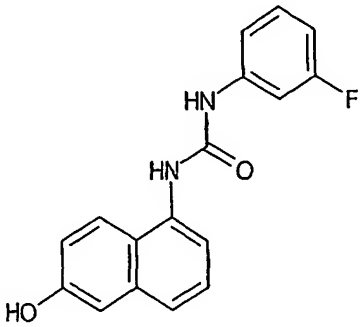
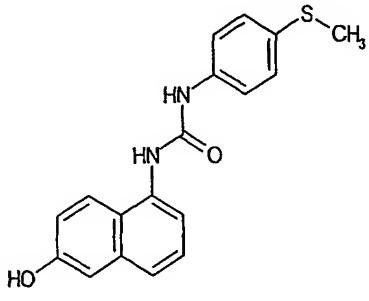
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-150		408,8109	409	
1-151		370,4115	371	
1-152		328,3739	329	
1-153		346,3117	347	
1-154		347,2034	347	

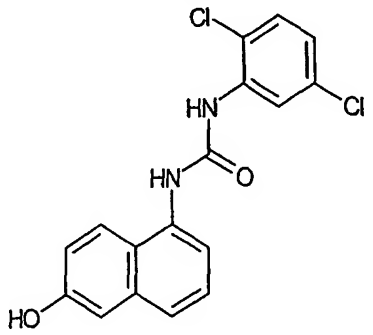
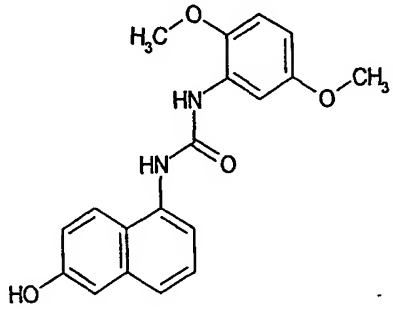
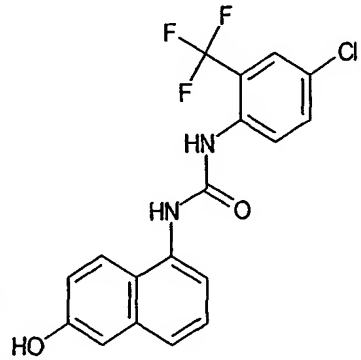
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-155		341,3013	342	
1-156		323,3109	324	
1-157		350,3775	351	
1-158		357,2094	359	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-159		292,3404	293	
1-160		312,7584	313	
1-161		347,2034	347	
1-162		320,351	321	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-163		323,3109	324	
1-164		420,8221	421	183-184
1-165		484,8661	485	220-222
1-166		416,8677	417	214-215
1-167		408,8109	409	

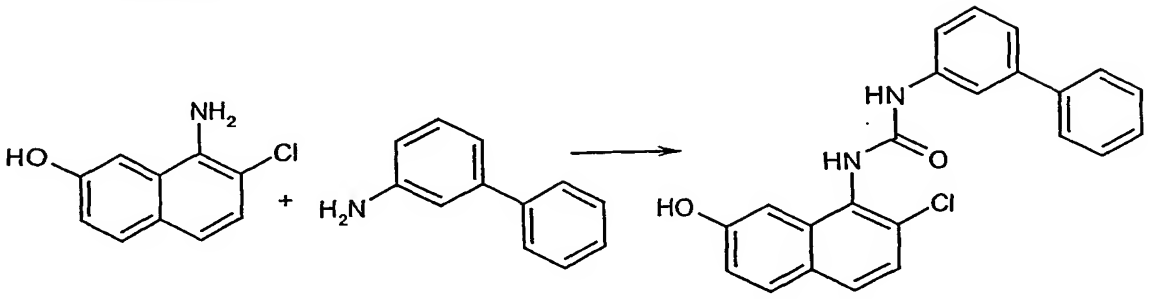
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-168		346,3117	347	
1-169		312,7584	313	
1-170		326,7855	327	
1-171		347,2034	347	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-172		347,2034	347	
1-173		380,7567	381	
1-174		296,3038	297	
1-175		324,4044	325	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
1-176		347,2034	347	
1-177		338,3663	339	
1-178		380,7567	381	

Example 2-1

N-(1,1'-Biphenyl-3-yl)-N'-(2-chloro-7-hydroxy-1-naphthyl)urea



This example was performed according to the general method B.

To the solution of 8-amino-7-chloro-2-naphthol(starting compound F) (67.77 mg, 0.35 mmol) and pyridine (0.04 mL, 0.44 mmol) in THF (1 mL) was added phenyl chloroformate (57.93 mg, 0.37 mmol) at room temperature. The mixture was stirred for 1 hour at room temperature. To the reaction mixture was added ethylacetate and washed with water and brine. The organic layer was concentrated *in vacuo*. To the residue was added DMSO (1 mL) and then added a 3-aminobiphenyl at room temperature. The mixture was stirred for 16 hours at 100°C. To the mixture was added water, and the precipitate was filtered and washed with diisopropyl ether to give N-(1,1'-biphenyl-3-yl)-N'-(2-chloro-7-hydroxy-1-naphthyl)urea (102.1 mg, 87.5 %).

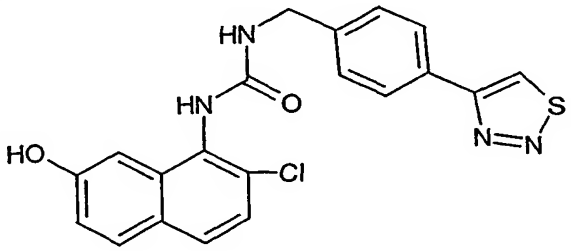
Molecular weight 388.86

MS (M+H):389

mp: 234-236°C

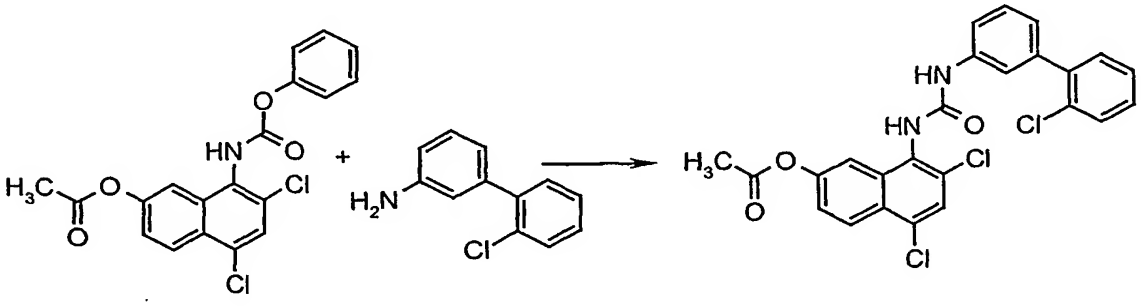
With the use of the starting material F and according to the similar procedure of Example 2-1, the following compound was synthesized and tested.

Table 2

Ex. No.	MOL STRUCTURE	MW	MS	Melting Point
2-2		410.89	nd	241-244

Example 3-1

5,7-Dichloro-8-({[(2'-chloro-1,1'-biphenyl-3-yl)amino]carbonyl}amino)-2-naphthyl acetate



This example was performed according to the general method C.

A mixture of 5,7-dichloro-8-[(phenoxycarbonyl)amino]-2-naphthyl acetate (starting compound K) (762 mg, 2.0 mmol) and 2'-chloro-biphenyl-3-ylamine (407 mg, 2.0 mmol) in DMSO (6 mL) was stirred for 5 hours at 100°C. To the reaction mixture was added water, the precipitate was filtered and dried to give acetic acid 5,7-dichloro-8-({[(2'-chloro-1,1'-biphenyl-3-yl)amino]carbonyl}amino)-2-naphthyl acetate (805 mg, 81 %).

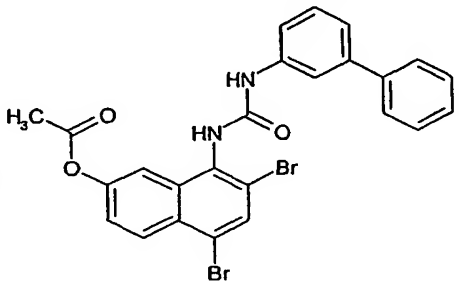
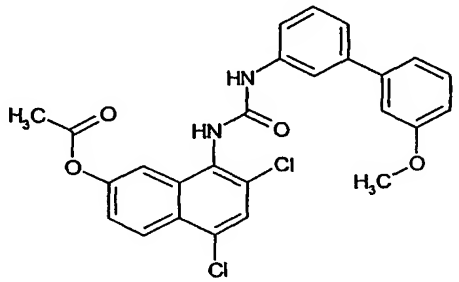
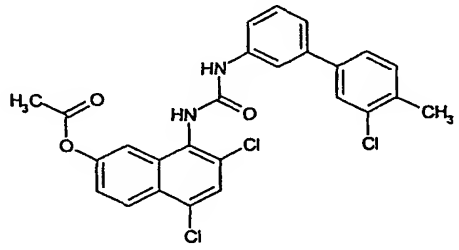
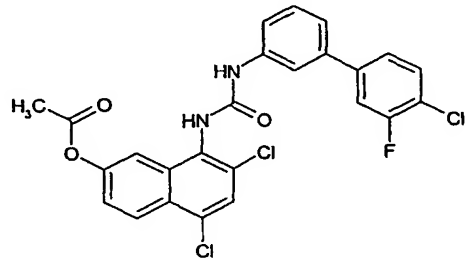
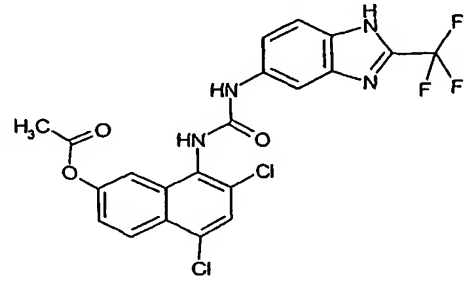
Molecular weight 499.78

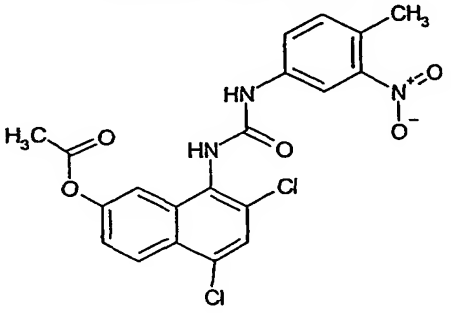
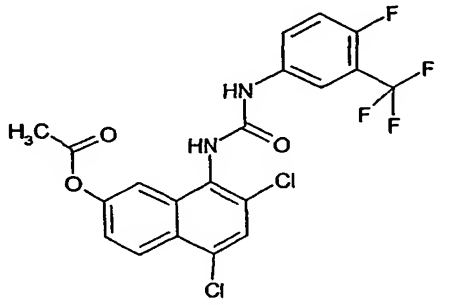
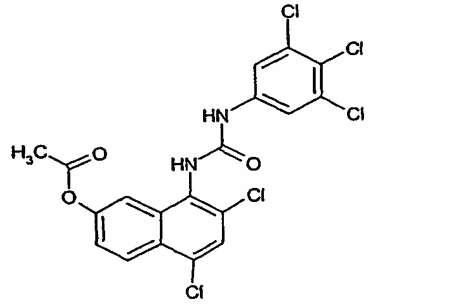
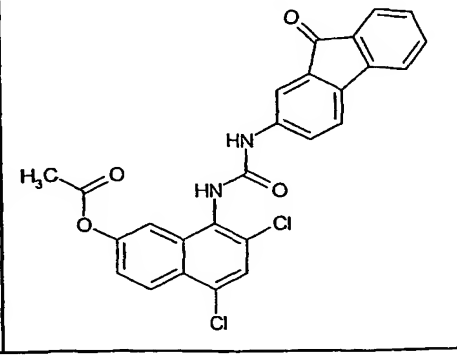
mp: 180°C

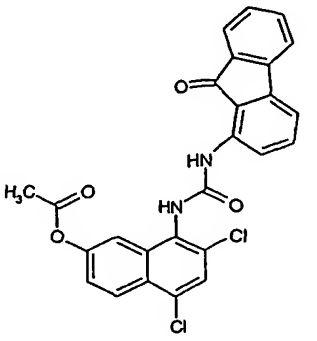
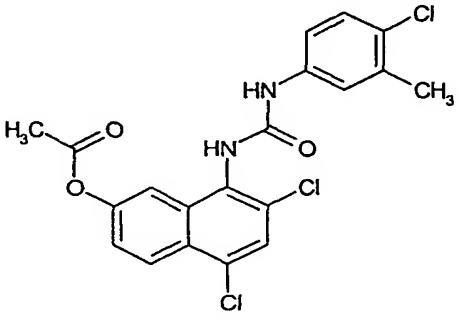
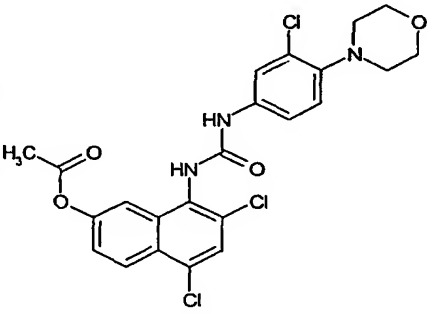
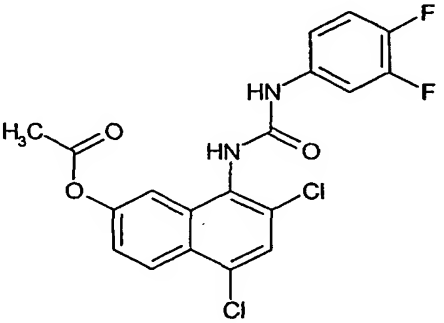
With the use of the starting material K and according to the similar procedure of Example 3-1, the following compounds were synthesized and tested.

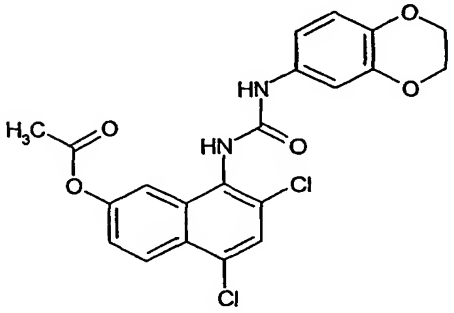
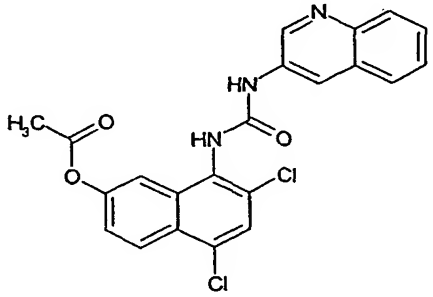
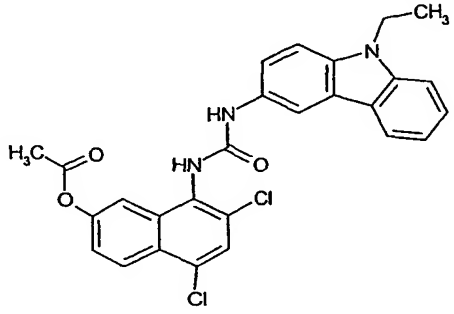
5

Table 3

Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
3-2		554.24181	555	235-Z
3-3		495.3663	495,497	224Z
3-4		513.81193	513,515	260
3-5		517.77527	517,519	287
3-6		497.26396	497	210 Z

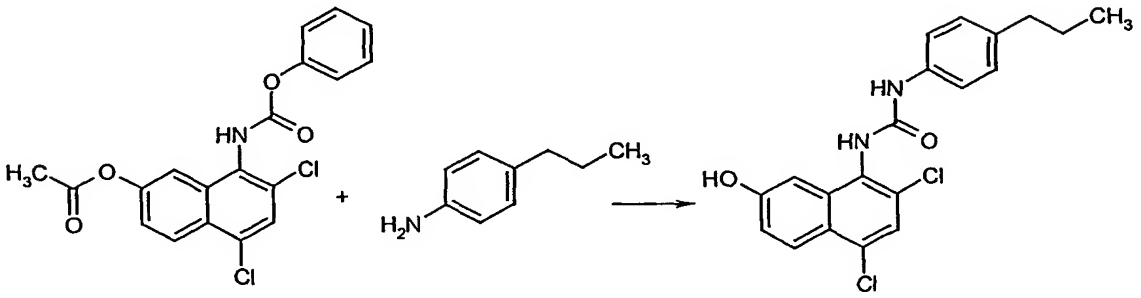
Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
3-7		448.26565	448	210 Z
3-8		475.22984	475	209 Z
3-9		492.57612	491	235 Z
3-10		491.33442	491,493	213-Z

Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
3-11		491.33442	491	ND
3-12		437.71315	437	ND
3-13		508.79255	508,510	206
3-14		425.22189	425,427	226-Z

Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
3-15		447.27807	nd	240Z
3-16		440.28915	440,442	205-Z
3-17		506.39272	506	260 Z

Example 4-1

N-(2,4-Dichloro-7-hydroxy-1-naphthyl)-N'-(4-propylphenyl)urea



This example was performed according to the general method D.

(1) A mixture of 5,7-dichloro-8-[(phenoxycarbonyl)amino]-2-naphthyl acetate (starting compound K) (195.11 mg, 0.5 mmol) and 4-propylaniline (67.61 mg, 0.5 mmol) in DMSO (1.5 mL) was stirred for 5 hours at 100 °C. To the reaction mixture was added water, the precipitate was filtered and dried to give 5,7-dichloro-8-({[(4-propylphenyl)amino]carbonyl}amino)-2-naphthyl acetate (88.4 mg, 41 %).

(2) Next, a mixture of 5,7-dichloro-8-({[(4-propylphenyl)amino]carbonyl}-amino)-2-naphthyl acetate (88.0 mg, 0.2 mmol) and potassium carbonate (207 mg) in methanol (6 mL) was heated at 50°C for 14 hours. After filtration, the mixture was concentrated *in vacuo*. The residue was washed with water, filtrated, and dried. To the obtained solid was added Dowex (492 mg) and methanol (4 mL), and the mixture was heated at 50°C for 3 hours. To the mixture was added acetone and then filtrated. After washed with acetone, the filtrate was concentrated *in vacuo*. The residue was washed with diisopropyl ether to give N-(2,4-dichloro-7-hydroxy-1-naphthyl)-N'-(4-propylphenyl)urea (52.7 mg, 66 %).

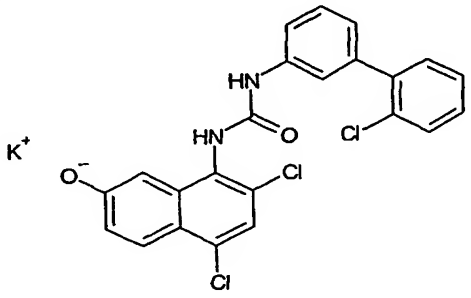
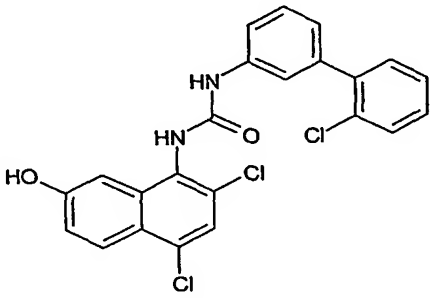
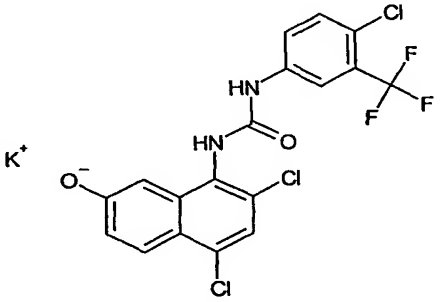
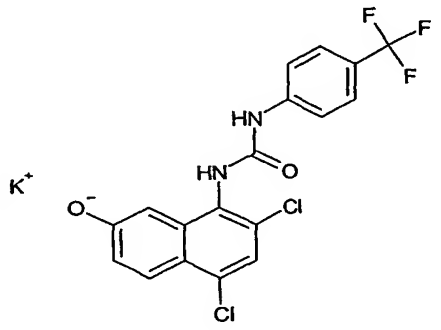
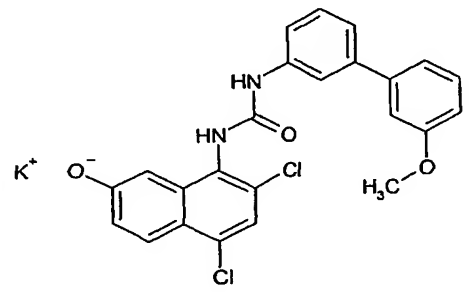
Molecular weight 389.28

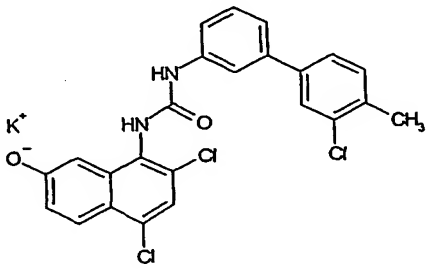
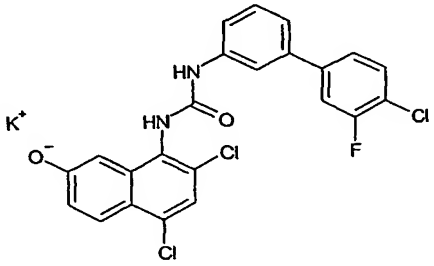
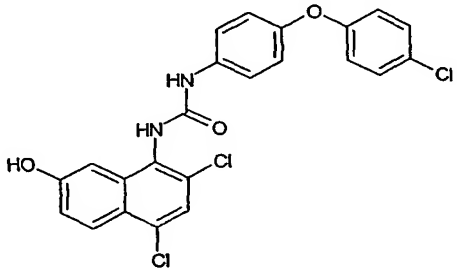
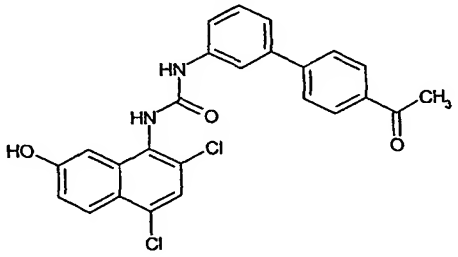
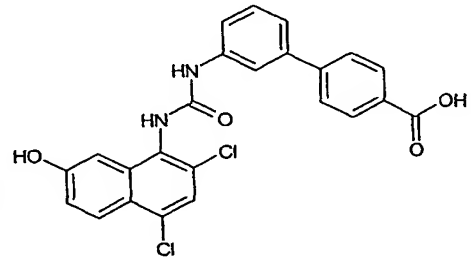
MS (M+H):389

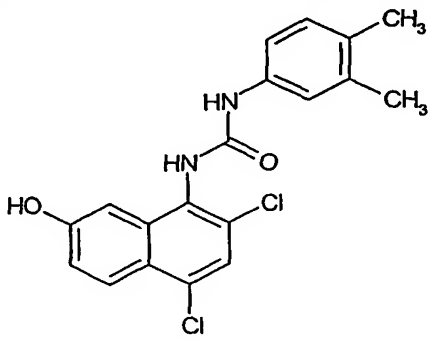
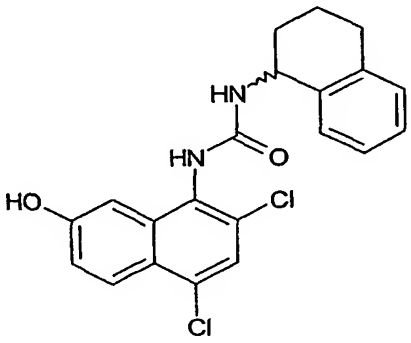
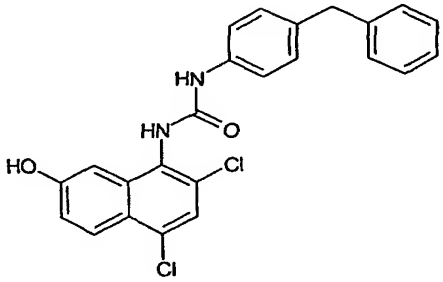
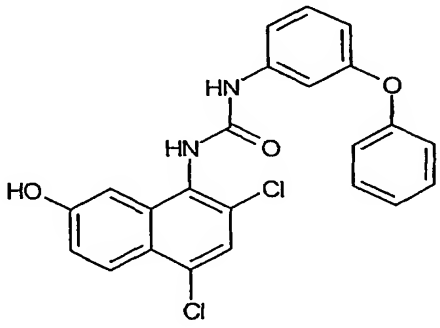
mp: 241°C

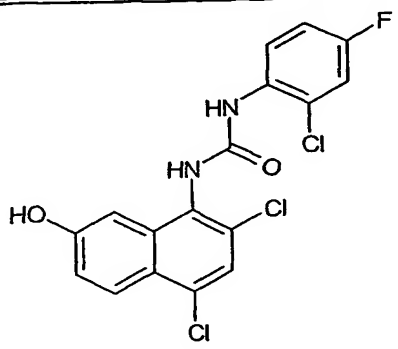
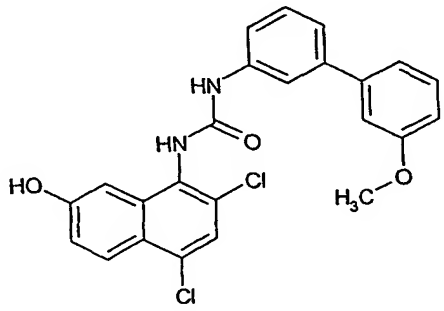
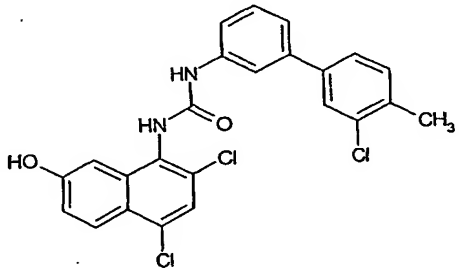
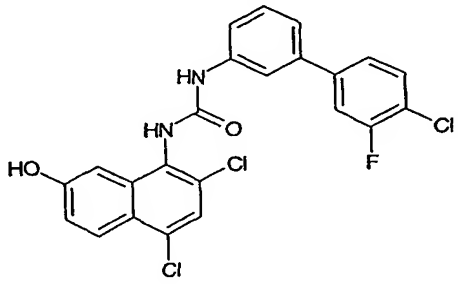
With the use of the starting material K and according to the similar procedure of Example 4-1 (1) to (3), or (1) to (2) (potassium salts), the following compounds were synthesized and tested.

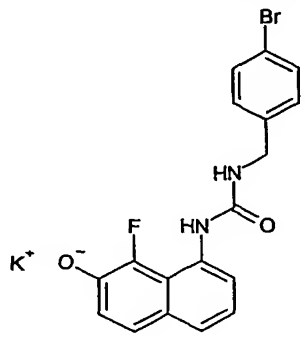
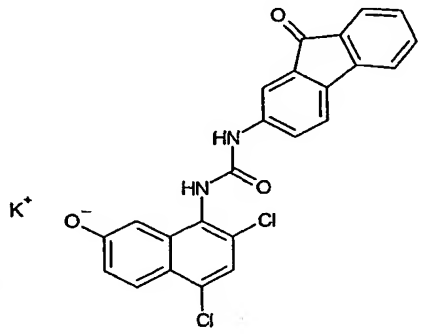
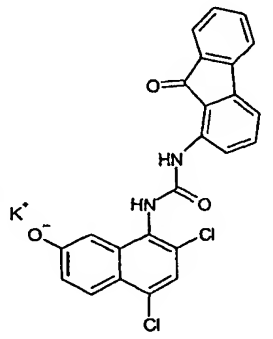
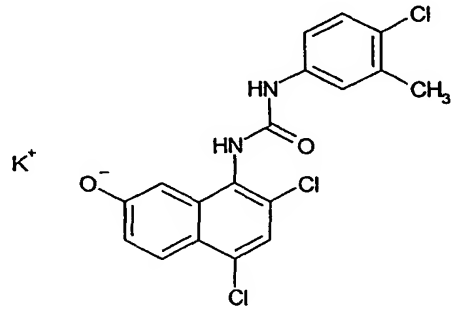
Table 4

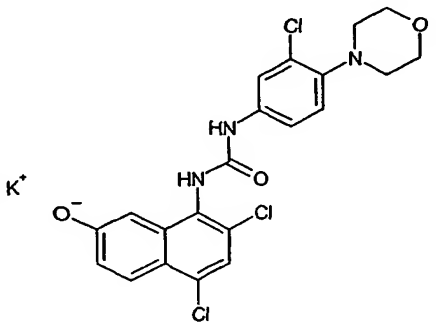
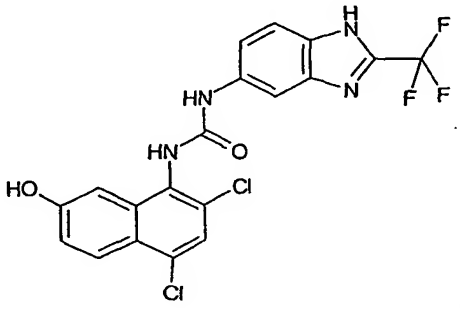
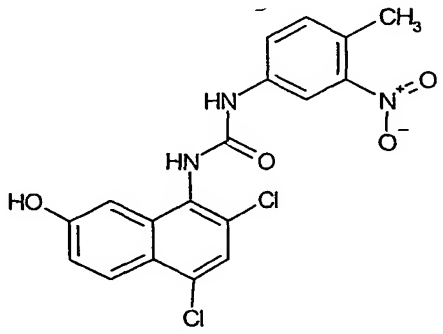
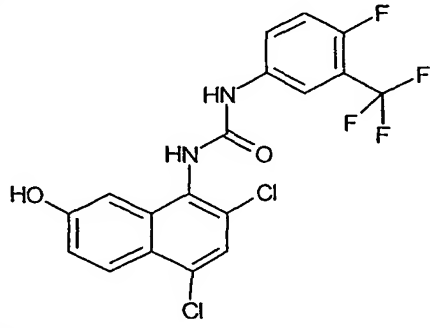
Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-2		495.84123	nd	209 Z
4-3		457.7472	457	228-232
4-4		487.74083	nd	150-Z
4-5		453.2958	nd	179-Z
4-6		491.42269	453,455	206-Z

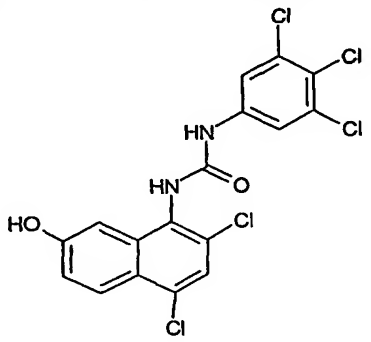
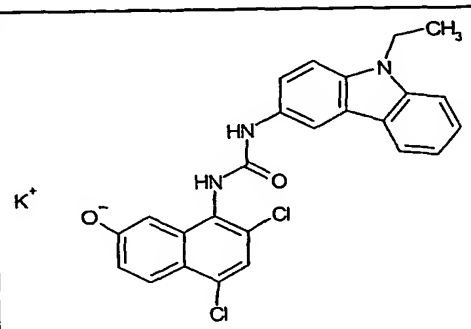
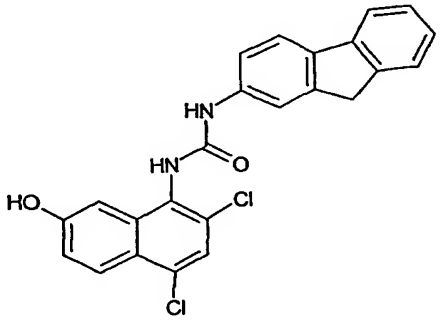
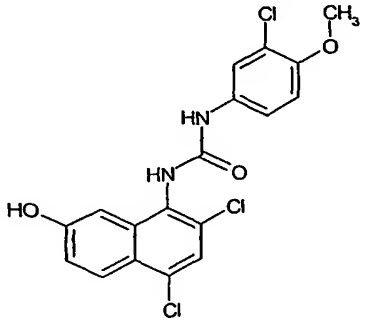
Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-7		509.86832	511	203-Z
4-8		513.83166	470,472	174-Z
4-9		473.7466	nd	230
4-10		465.33981	nd	253
4-11		467.31212	nd	247-Z

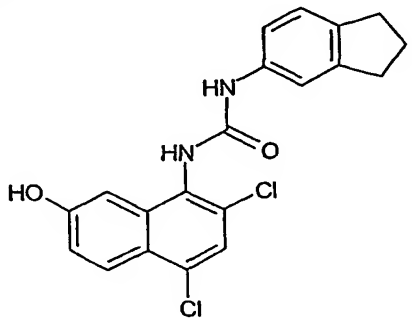
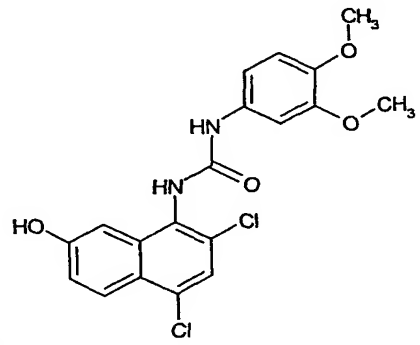
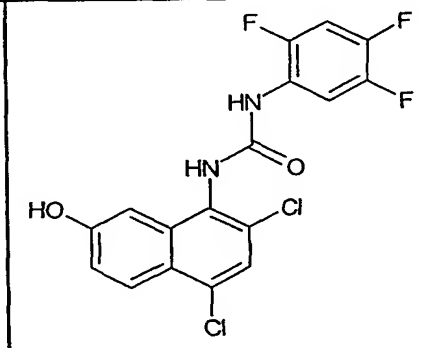
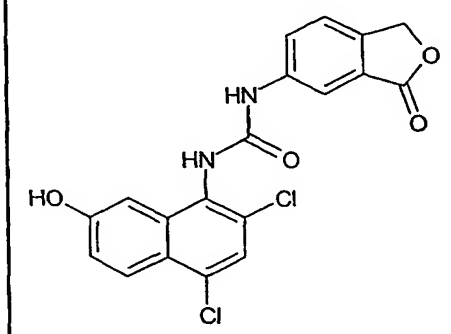
Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-12		375.25757	375, 377	239-Z
4-13		401.29581	nd	238-Z
4-14		437.32926	437, 439	230-Z
4-15		439.30157	439	226-Z

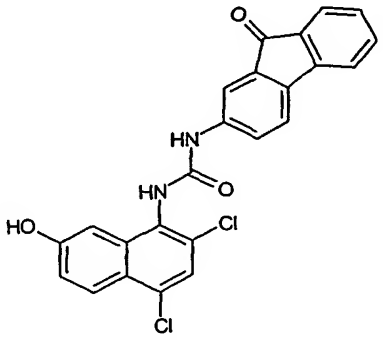
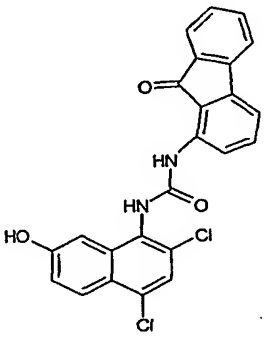
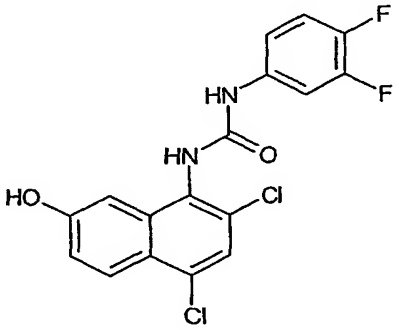
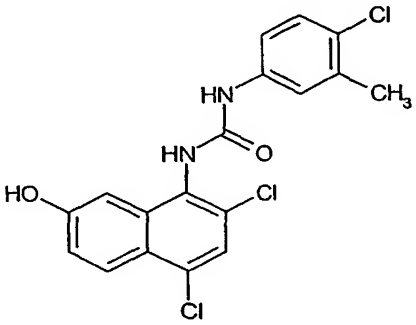
Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-16		399.63885	399	298-Z
4-17		453.32866	nd	246-Z
4-18		471.77429	nd	234-Z
4-19		475.73763	nd	241-Z

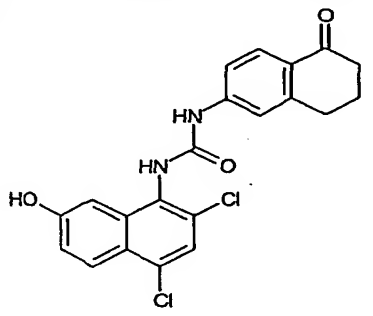
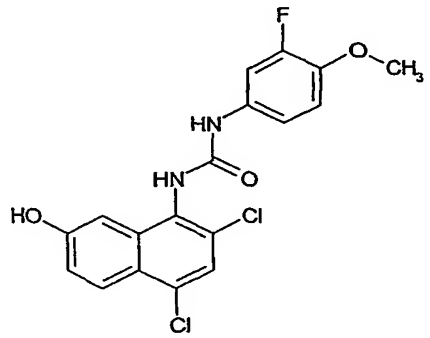
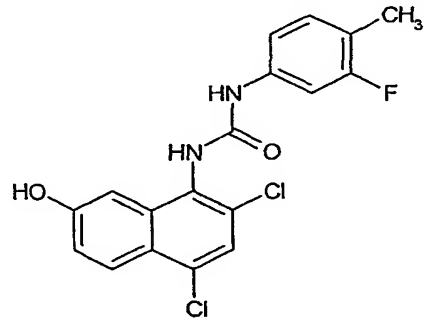
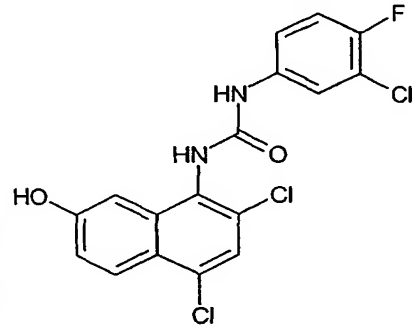
Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-20		427.32091	-	185
4-21		487.39081	449,451	200
4-22		487.39081	449,451	195
4-23		433.76954	395,397	190

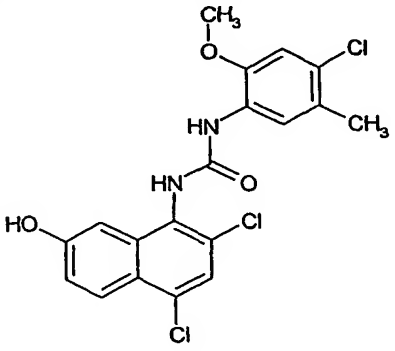
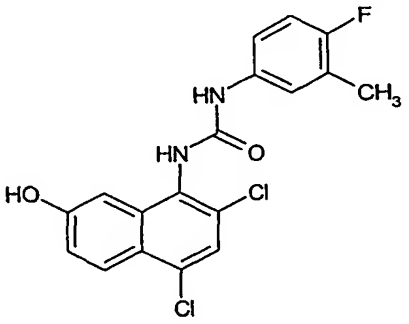
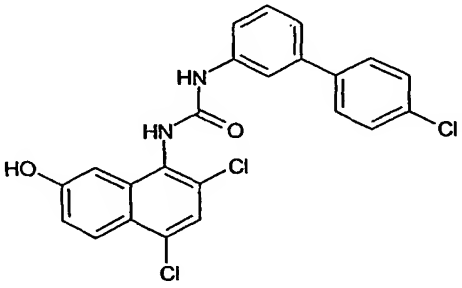
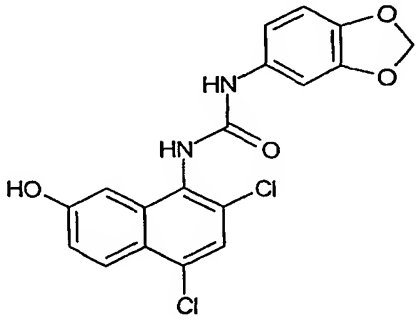
Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-24		504.84894	466,468	188
4-25		455.22632	455	ND
4-26		406.22801	406	250 Z
4-27		433.1922	433	228 Z

Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-28		450.53848	nd	251 Z
4-29		502.44911	464(free)	188 Z
4-30		435.31332	435	250 Z
4-31		411.67491	412	259Z

Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-32		387.26872	389	>300
4-33		407.25637	409	255Z
4-34		401.17468	nd	306Z
4-35		403.22449	404	290-291Z

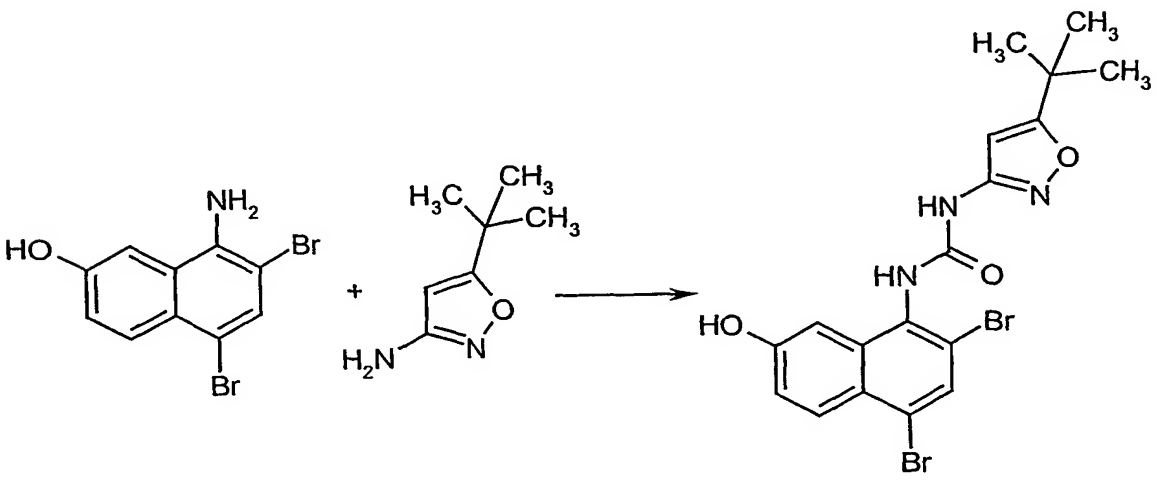
Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-36		449.29678	449,451	236-Z
4-37		449.29678	449,451	>250
4-38		383.18425	382,384	244-Z
4-39		395.67551	395,397	240-Z

Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-40		415.27927	415,417	230-Z
4-41		395.22031	395	235-238Z
4-42		379.22091	381	261-264Z
4-43		399.63885	nd	>229Z

Ex.No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
4-44		425.702	425, 427	>259Z
4-45		379.22091	379, 381	250-252Z
4-46		457.7472	nd	>231Z
4-47		391.21334	393	>260z

Example 5-1

N-(5-tert-Butyl-3-isoxazolyl)-N'-(2,4-dibromo-7-hydroxy-1-naphthyl)urea



This example was performed according to the general method E.

To a suspension of 1,1'-carbonyldi(1,2,4-triazole)(CDT) (51.8 mg, 0.315 mmol) in THF (1 mL), was added 5-tert-butyl-isoxazol-3-ylamine (44.2 mg, 0.315 mmol) at room temperature. The resulting suspension was stirred for 1 hour.

To the mixture was added 8-amino-5,7-dibromo-2-naphthol (starting compound I) (100 mg, 0.315 mmol) at room temperature and was stirred for 15 hours. The solvent was removed under reduced pressure. The residue was dissolved in a mixture of ethyl acetate, and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Hexane was added and the precipitate was filtered and washed with diethylether to give N-(5-tert-butyl-3-isoxazolyl)-N'-(2,4-dibromo-7-hydroxy-1-naphthyl)urea (20.5 mg, 13 %).

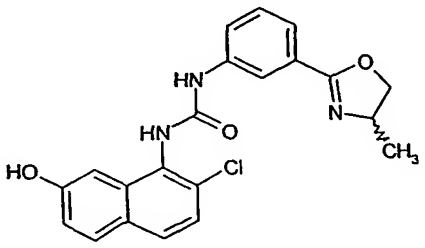
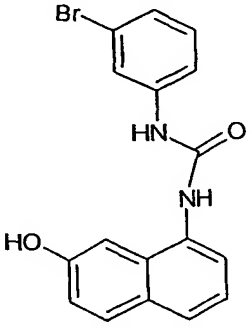
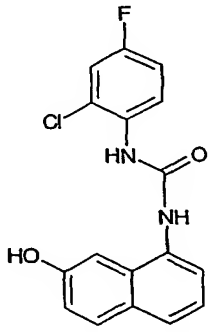
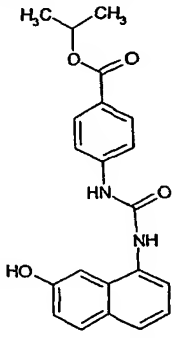
Molecular weight 483.16

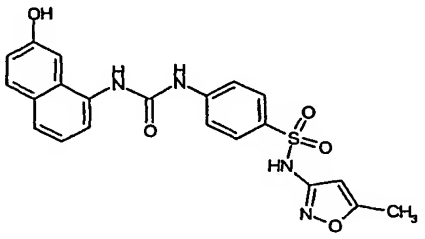
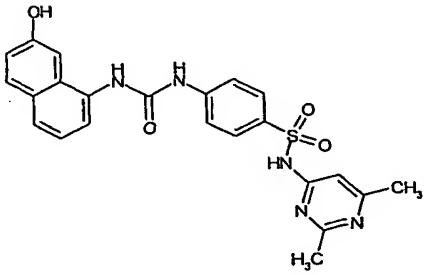
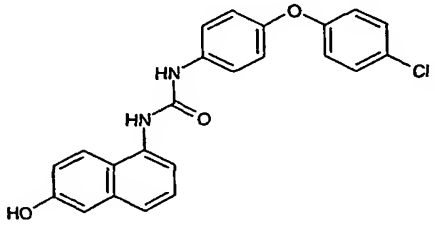
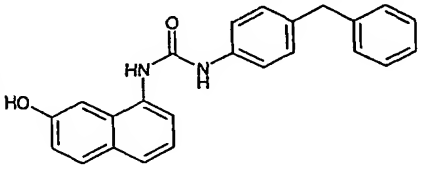
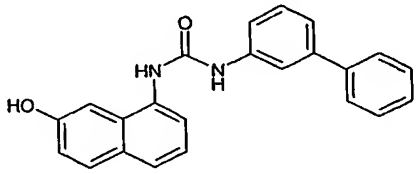
MS (M+H):484

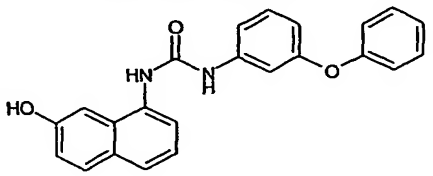
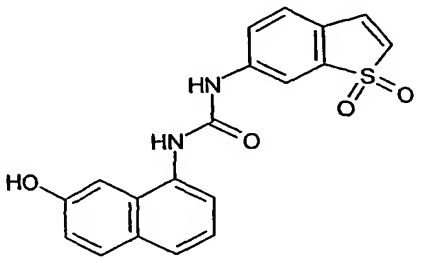
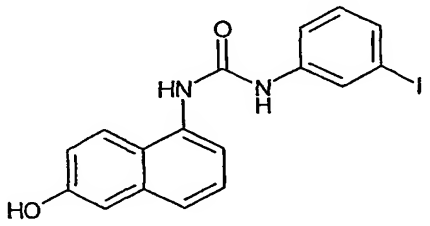
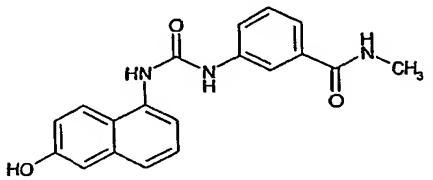
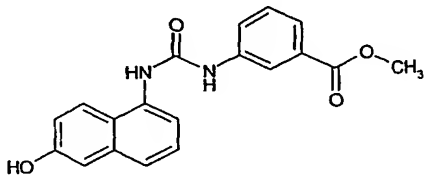
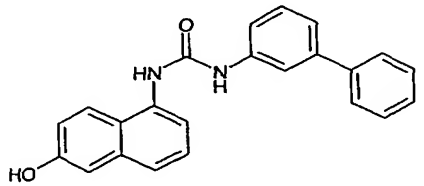
mp: 214.5°C

With the use of any of the starting materials A-E, G ,or I and according to the similar procedure of Example 5-1, the following compounds were synthesized and tested.

Table 5

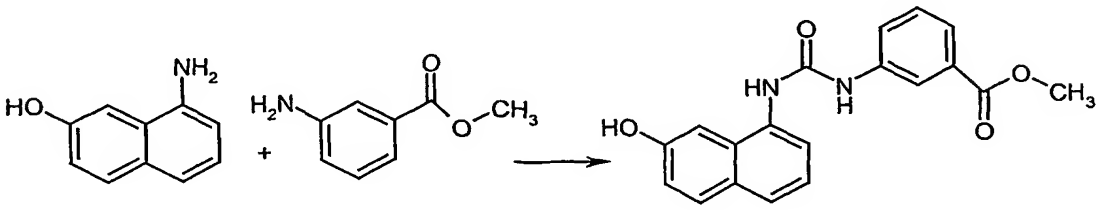
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
5-2		395.84891	396	162-Z
5-3		357.20936	359	
5-4		330.74879	331	
5-5		364.40455	365	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
5-6		438.46541	439	
5-7		463.51892	464	
5-8		404.85654	405	
5-9		368.4392	369	
5-10		354.41211	355	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
5-11		370.41151	371	
5-12		366.39843	367	
5-13		404.20976	405	
5-14		335.36564	336	
5-15		336.35037	337	
5-16		354.41211	355	

Example 6-1

Methyl 3-({[(7-hydroxy-1-naphthyl)amino]carbonyl}amino)benzoate



This example was performed according to said method F.

To a suspension of 1,1'-carbonyldi(1,2,4-triazole)(CDT) (65.7mg, 0.4mmol) in THF (0.8 ml), was added a solution of 1-amino-7-naphthol (63.7mg, 0.4mmol) in THF (0.8 ml) at room temperature dropwise. The resulting suspension was stirred for 1 hour.

Methyl 3-aminobenzoate (60.5mg, 0.4mmol) was added to the suspension at room temperature. The reaction mixture was stirred at 50°C for 15hrs. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in a mixture of ethyl acetate and ethanol (1:1), and it was passed through a silicagel short cartridge (1g Si / 6ml). The cartridge was washed with a mixture of ethyl acetate and ethanol (1:1). The combined filtrates were concentrated to give the dark purple solid.

The crude product was washed with a mixture of isopropanol and isopropyl ether to give methyl 3-({[(7-hydroxy-1-naphthyl)amino]carbonyl}amino)benzoate as grayish purple powder (57.5mg, 42%).

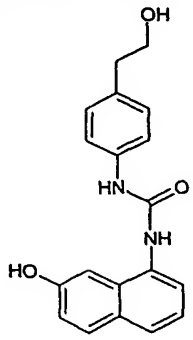
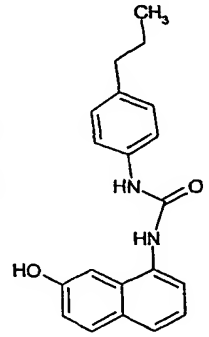
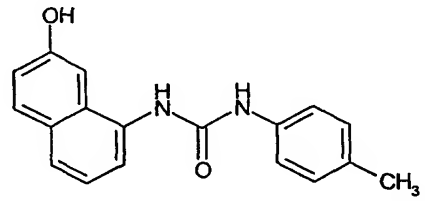
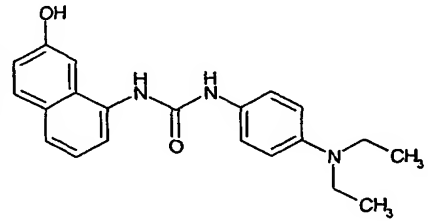
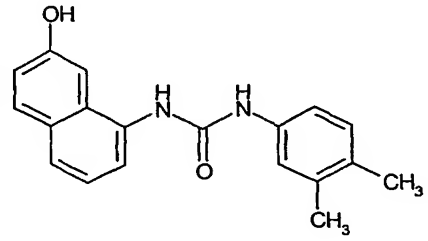
Molecular weight 336.3504

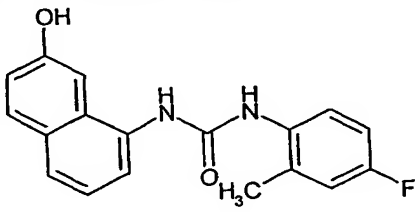
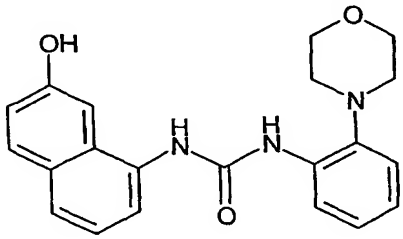
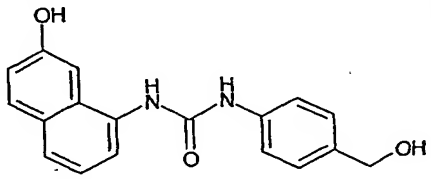
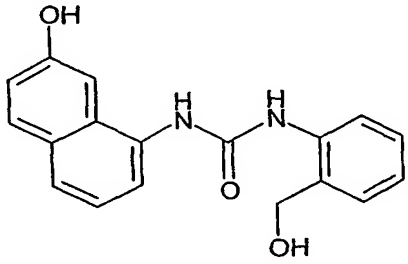
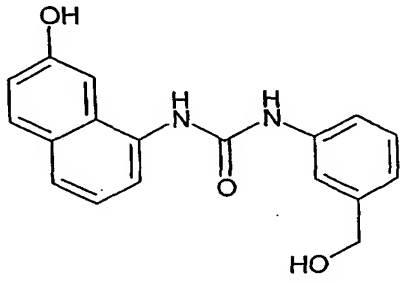
MS (M+H):337

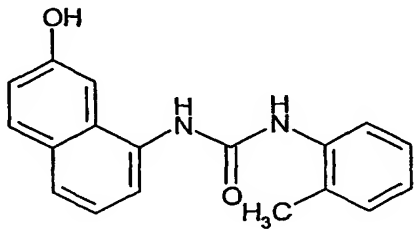
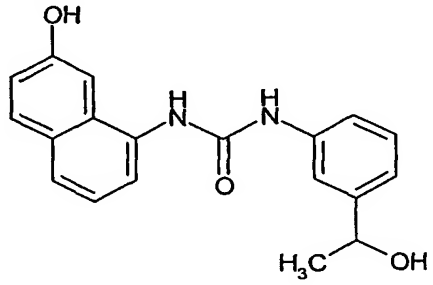
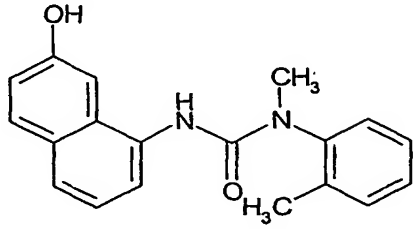
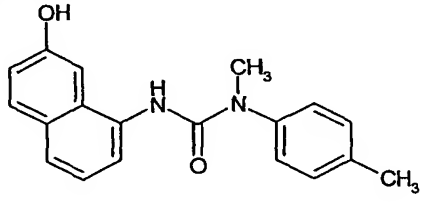
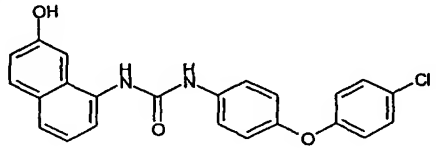
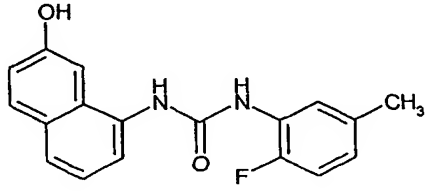
Activity grade

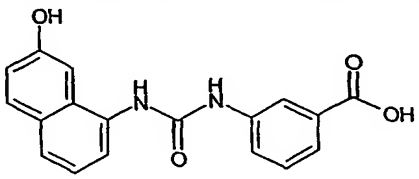
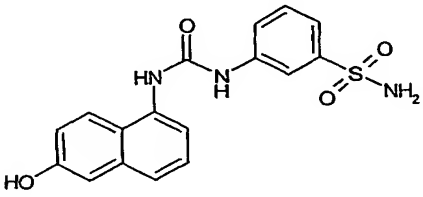
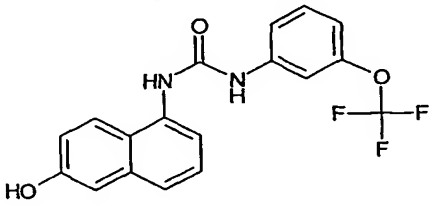
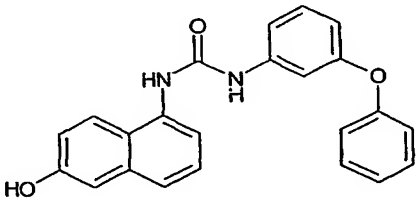
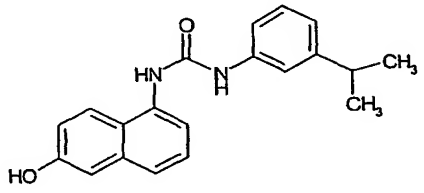
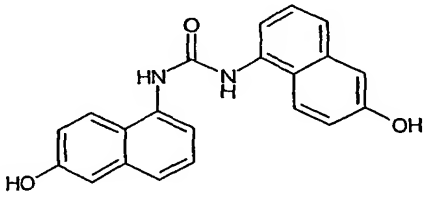
With the use of any of the starting materials A-E or 1-aminonaphtol and according to the similar procedure of Example 6-1, the following compounds were synthesized and tested.

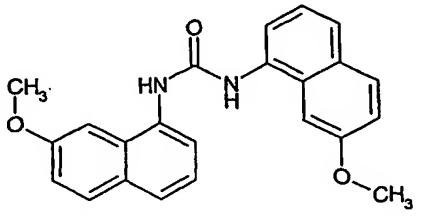
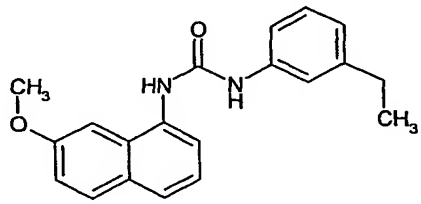
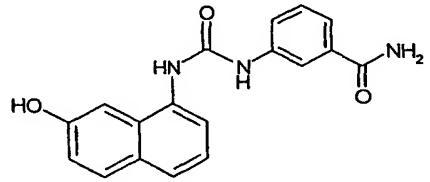
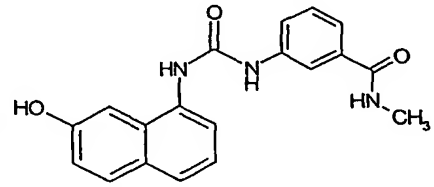
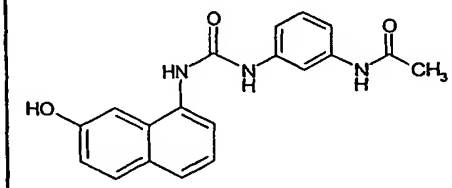
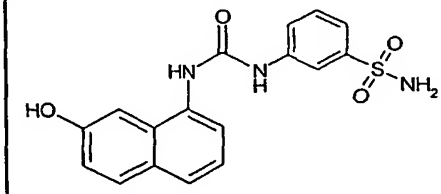
Table 6

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
6-2		322.36691	323	
6-3		320.3946	321	
6-4		292.34042	293	
6-5		349.43636	350	
6-6		306.36751	307	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
6-7		310.33085	311	
6-8		363.41982	364	
6-9		308.33982	309	
6-10		308.33982	309	
6-11		308.33982	309	

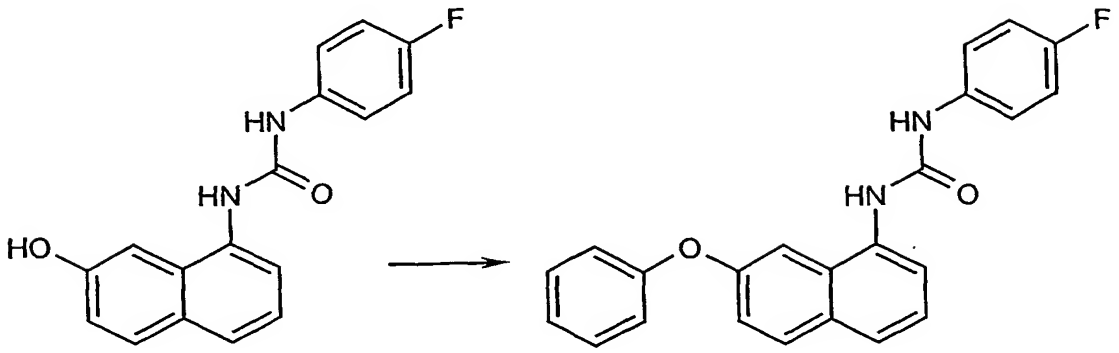
Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
6-12		292.34042	293	
6-13		322.36691	323	
6-14		306.36751	307	
6-15		306.36751	307	
6-16		404.85654	405	
6-17		310.33085	311	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
6-18		322.32328	323	
6-19		357.3908	358	
6-20		362.31111	363	
6-21		370.41151	371	
6-22		320.3946	321	
6-23		344.37327	345	

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
6-24		372.42745	373	
6-25		320.3946	321	
6-26		321.33855	322	
6-27		335.36564	336	
6-28		335.36564	336	
6-29		357.3908	358	

Example 7-1

N-(4-Fluorophenyl)-N'-(7-phenoxy-1-naphthyl)urea



Using said reaction G performed this example.

To a stirred suspension of N-(4-fluorophenyl)-N'-(7-hydroxy-1-naphthyl)urea (0.100 g, 0.337 mmol) obtained in the Example 1-88, phenylboronic acid (0.082 g, 0.675 mmol), copper(II) acetate (0.061 g, 0.337 mmol) and molecular sieves 4A (0.100 g) in dichloromethane (3.5 mL) was added triethylamine (0.240 mL, 1.687 mmol). The mixture was stirred at room temperature for 18 hrs, then passed through a celite pad. The filtrate was concentrated under reduced pressure. The resulting residue was triturated with isopropyl ether to give N-(4-fluorophenyl)-N'-(7-phenoxy-1-naphthyl)urea (0.088 g, 70%).

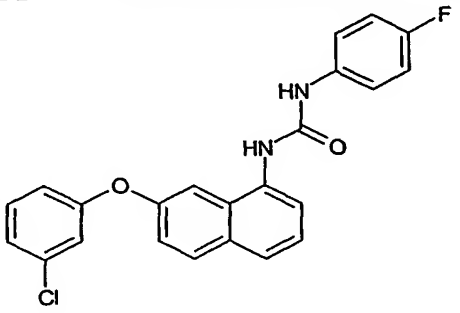
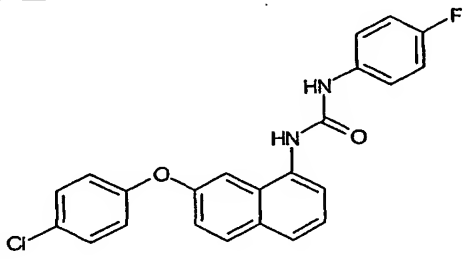
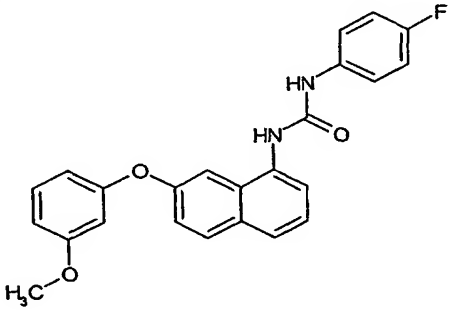
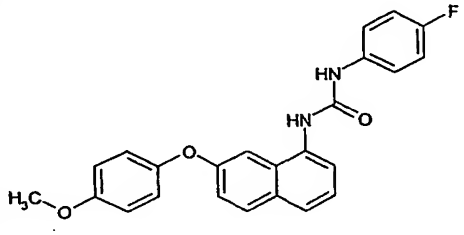
Molecular weight 372.4025

MS (M+H):373

Activity grade:D

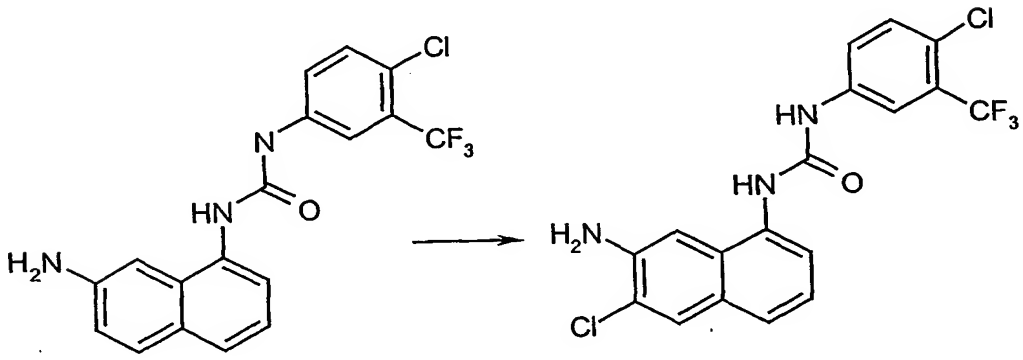
With the use of any of the compound prepared in Example 1, 5, or 6 and according to the similar procedure of Example 7-1, the following compounds were synthesized and tested.

Table 7

Ex class	MOLSTRUCTURE	MW	MS	Melting Point (°C)
7-2		406.84757	407	
7-3		406.84757	407	
7-4		402.42903	403	
7-5		402.42903	403	

Example 8-1

N-(7-Amino-6-chloro-1-naphthyl)-N'-(4-chloro-3-methylphenyl)urea



This example was performed according to the general method H.

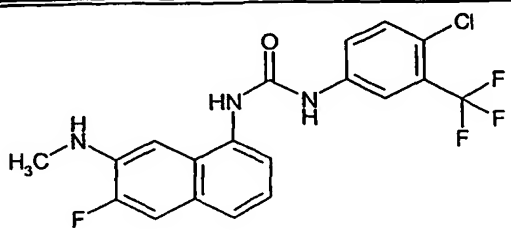
A solution of N-(7-amino-naphthalen-1-yl)-N'-(4-chloro-3-trifluoromethyl-phenyl)-urea obtained in the Example 1-76, (46.5 mg, 0.122 mmol) in tetrahydrofuran (7 mL) was added N-chlorosuccinimide (20.7 mg, 0.155 mmol) at 0°C, and the mixture was stirred for 2 hours. The mixture was concentrated under reduced pressure and was purified by silica gel column chromatography (hexane:ethylacetate, 1:2) to give N-(7-amino-6-chloro-1-naphthyl)-N'-(4-chloro-3-methylphenyl)urea (8.80 mg, 17% yield).

Molecular weight 414.22

MS (M+H):415

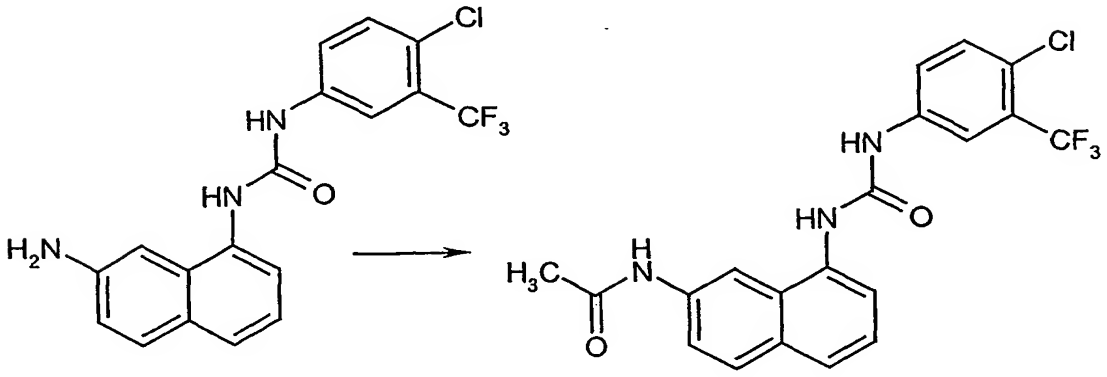
mp: 242°C

Table 8

Ex. No	MOLSTRUCTURE	MW	MS	Melting Point (°C)
8-2		411.78953	412	209-210

Example 9-1

N-{8-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthyl}acetamide



This example was performed according to the general method I.

A mixture of N-(7-amino-1-naphthyl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea, obtained in the Example 1-76, (50.0 mg, 0.132 mmol) and acetic anhydride (27.3 mg, 0.260 mmol) in pyridine (5 mL) was stirred at 50°C for 3 hours. To the mixture was added saturated aqueous solution of sodium bicarbonate, stirred for 1 hour, and extracted with ethylacetate. The organic layer was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethylacetate, 1:2) to give N-{8-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthyl}acetamide (24.5 mg, 44 % yield).

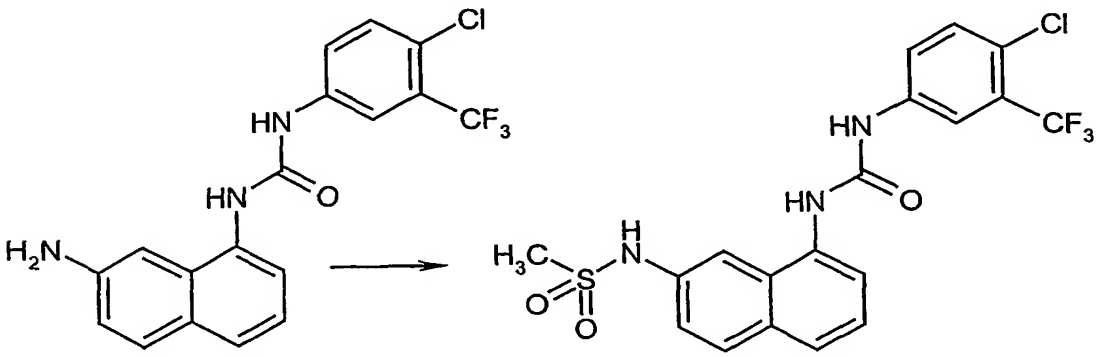
Molecular weight 421.81

MS (M+H):422

mp: 241-242°C

Example 10-1

N-{8-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthyl}methanesulfonamide



This example was performed according to the general method J.

To a mixture of N-(7-amino-1-naphthyl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]-urea, obtained in the Example 1-76, (38.0 mg, 0.100 mmol) and triethylamine (20.3 mg, 0.200 mmol) in tetrahydrofuran (10 mL) was added methanesulfonyl chloride (17.2 mg, 0.150 mmol) at 0°C. After stirred for 16 hours at room temperature, the mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethylacetate, 1:1) to give N-{8-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]-2-naphthyl}methanesulfonamide (18.8 mg, 41 % yield).

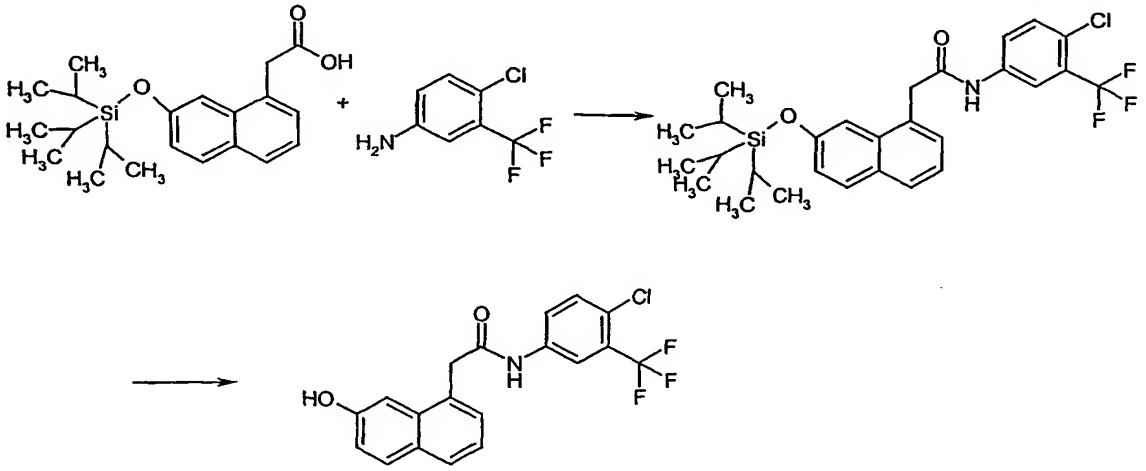
Molecular weight 457.86

MS (M+H):458

mp: 225-226°C

Example 11-1

N-[4-Chloro-3-(trifluoromethyl)phenyl]-2-(7-hydroxy-1-naphthyl)acetamide



This example was performed according to the general method K

To a mixture of {7-[(triisopropylsilyl)oxy]-1-naphthyl}acetic acid (Starting compound P) (12.0 mg, 0.033 mmol), 4-chloro-3-trifluoromethyl aniline (8.0 mg, 0.040 mmol), and 4-dimethylaminopyridine (1.0 mg, 0.007 mmol) in dichloromethane (1.0 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (8.0 mg, 0.040 mmol) at room temperature, and stirred for 16 hours. To the mixture was added ethylacetate and the organic layer was washed with aqueous 1 N hydrochloric acid, aqueous 1 N sodium hydroxide, water, then with brine. The organic layer was dried over MgSO4, filtered, and concentrated under reduces pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethylacetate, 10:1) to give N-[4-chloro-3-(trifluoromethyl)phenyl]-2-{7-[(triisopropylsilyl)oxy]-1-naphthyl}acetamide (16.0 mg, 89 % yield).

Next, to a solution of N-[4-chloro-3-(trifluoromethyl)phenyl]-2-{7-[(triisopropylsilyl)oxy]-1-naphthyl}acetamide (16.0 mg, 0.030 mmol) in tetrahydrofuran (1.0 mL) was added 1M tetrabutylammonium fluoride in THF (1.0 mL) at room temperature. The mixture was stirred for 30 minutes at room temperature. The solvent was

removed under reduces pressure, and water was added. The product mixture was extracted with ethylacetate, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethylacetate, 4:1) to give N-[4-chloro-3-(trifluoromethyl)phenyl]-2-(7-hydroxy-1-naphthyl)acetamide (6.0 mg, 65 % yield).

Molecular weight 379.77

MS (M+H):380

mp: 162°C

***In vitro* profile of VR1 antagonists (Assays 1 to 3 and selectivity test)**

The compounds of the present invention inhibit the capsaicin-induced increase of intracellular calcium levels (Ca^{2+} flux) in the cell line expressing human VR1 in a concentration dependent manner with IC_{50} values. Functional activity (Ca^{2+} flux) in the capsaicin-stimulated rat DRG cells is inhibited by the tested compounds. Significant inhibition of the capsaicin-induced rat bladder detrusor contraction is observed for most of the tested compounds. Selectivity over other ion channel receptors such as P2X1 and P2X3 is high – more than 100 fold.

***In vivo* profile of VR1 antagonists (Assays 4 and 5)**

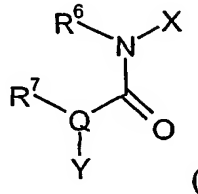
The effect of one of the compound of the present invention (VR1 antagonist) on the capsaicin-induced overactive bladder *in vivo* in anesthetized rats is investigated. The overactive bladder is induced by intravesical infusion of capsaicin solution. The frequency of the micturition is compared.

Intravenous administration of VR1 antagonist inhibits the capsaicin-induced increase of micturition reflex at 3 or 10 mg/kg.

As disclosed in assay 5, the effect of VR1 antagonists of the present invention on cyclophosamide induced cystitis in anesthetized rats is investigated. Significant improvement of both bladder capacity (Fig. 1 and Fig. 2) and micturition frequency (Fig. 1 and Fig. 3) is observed at a dosage of 0.5 mg/kg, i.v. and 5 mg/kg, i.v.

CLAIMS

(1) An amine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



(I)

wherein

X represents C_{3-8} cycloalkyl optionally fused by benzene, thienyl, thienyl C_{1-6} straight alkyl, quinolyl, 1,2-oxazolyl substituted by R^1, naphthyl optionally substituted by R^4 and R^5, phenyl fused by C_{4-8} cycloalkyl, phenyl fused by saturated C_{4-8} heterocycle having one or two O atoms, carbazolyl of which N-H is substituted by N-R^1, phenyl fused by indanone, phenyl fused by indan, phenyl fused by cyclohexanone, phenyl fused by dihydrofuranone, phenyl substituted by R^1, R^2 and R^3, phenyl C_{1-6} straight alkyl of which phenyl is substituted by R^1, R^2 and R^3, phenyl fused by unsaturated 5-6 membered hetero ring having one or two hetero atoms selected from the group consisting of N, O, S, and SO_2, wherein the hetero ring is optionally substituted by R^1,

wherein

R^1, R^2 and R^3 are identical or different and represent hydrogen, halogen, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkylcarbamoyl, carbamoyl, straight-chain or branched C_{1-6} alkoxy, carboxyl, nitro, amino, straight-chain or branched C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, morpholino, straight-chain or branched C_{1-6} alkoxycarbonyl, benzyl, phenoxy, halogen substituted phenoxy,

straight-chain or branched C_{1-6} alkylthio, straight-chain or branched C_{1-6} alkanoyl, straight-chain or branched C_{1-6} alkanoylamino, hydroxy substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkoxy, C_{1-6} alkyl substituted 4,5-dihydro-1,3-oxazolyl, 1,2,3-thiadiazolyl, the substituent represented by the formula $-SO_2-NH-R^{12}$ (R^{12} represents hydrogen, 5-methyl-isoxazole, or 2,4-dimethylpyrimidine) or

phenyl optionally substituted by one to three substituents,

wherein

the substituents are each identical or different and selected from the group consisting of hydrogen, halogen, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkanoyl, and carboxy;

R^4 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

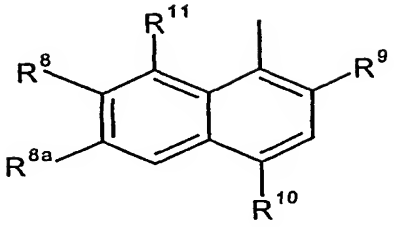
R^5 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

Q represents CH or N;

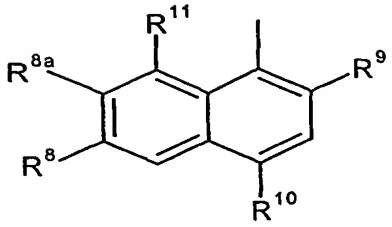
R^6 represents hydrogen or methyl;

R^7 represents hydrogen or methyl; and

Y represents

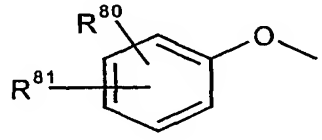


or



wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6}cyclo-alkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, C_{1-6} alkylsulfonamino, or the group represented by the formula



wherein

R^{80} and R^{81} are each identical or different and represent hydrogen, halogen, or straight-chain or branched C_{1-6} alkoxy;

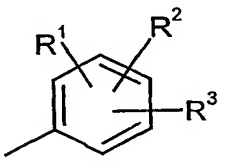
R^{8a} represents hydrogen or halogen;

R^9 and R^{11} are each identical or different and represent hydrogen, halogen, or nitro; and

R^{10} represents hydrogen, halogen, carboxy, carbamoyl, cyano, or straight-chain or branched C_{1-6} alkyl optionally substituted by the substituent, which substituent is selected from the group consisting of hydroxy, amino, di(straight-chain or branched C_{1-6} alkyl)amino, piperidino, morpholino, and methyl-piperazino.

(2) An amine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein

X represents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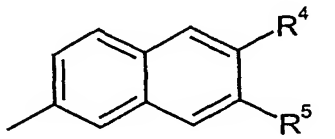
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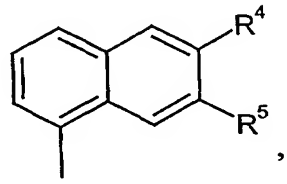
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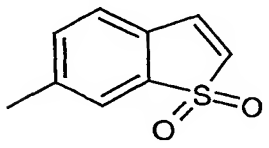
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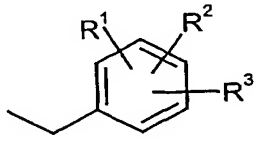
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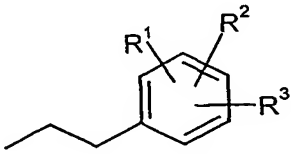
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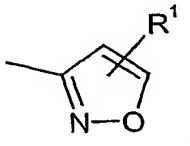
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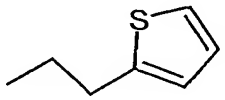
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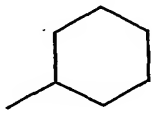
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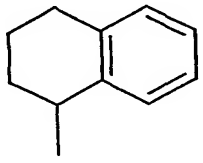
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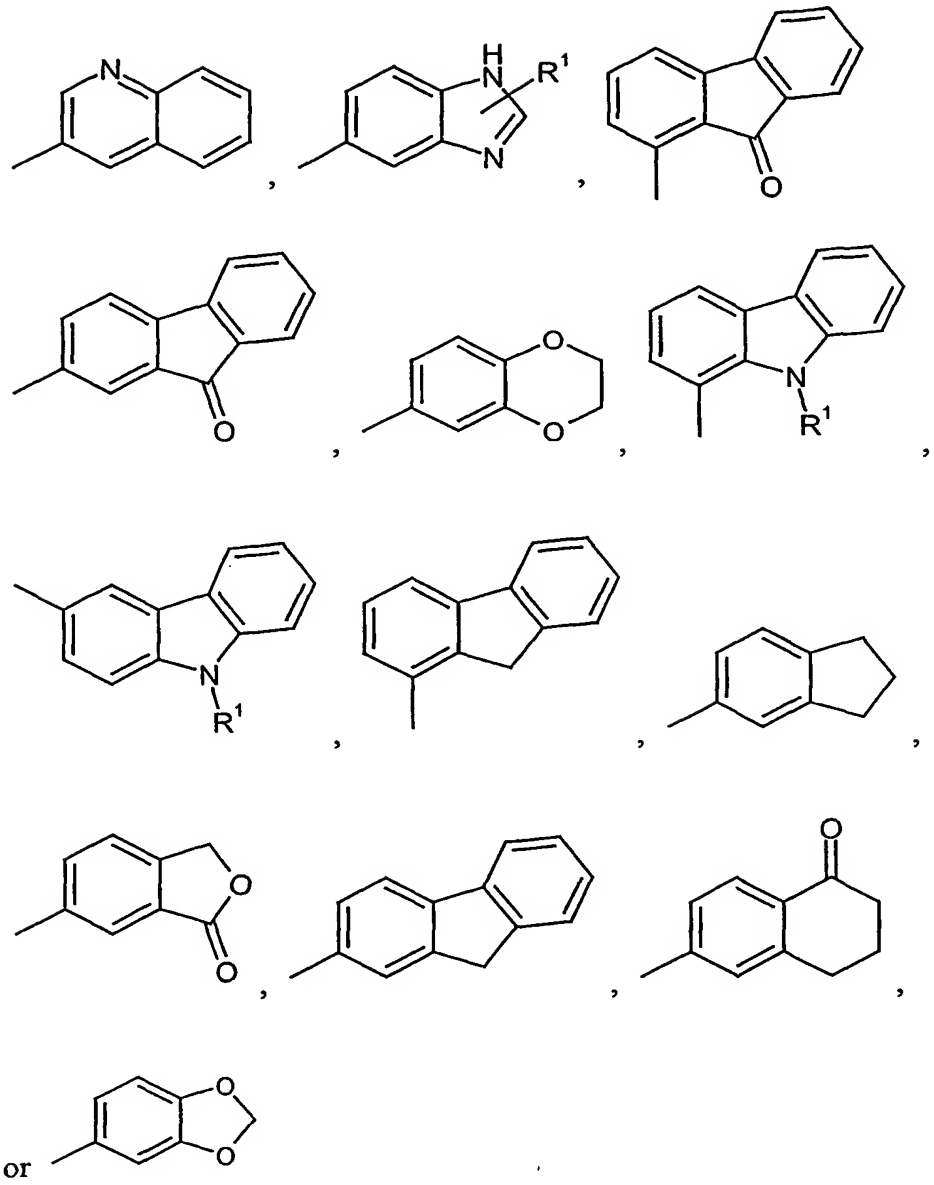


wherein

R^1, R^2 and R^3 are different or identical and represent hydrogen, halogen, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkylcarbamoyl, carbamoyl, straight-chain or branched C_{1-6} alkoxy, carboxyl, nitro, amino, straight-chain or branched C_{1-6} alkylamino, di(straight-chain or branched C_{1-6}

alkyl)amino, morpholino, straight-chain or branched C_{1-6} alkoxycarbonyl, benzyl, phenoxy, halogen substituted phenoxy, straight-chain or branched C_{1-6} alkylthio, straight-chain or branched C_{1-6} alkanoyl, straight-chain or branched C_{1-6} alkanoylamino, hydroxy substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkoxy, C_{1-6} alkyl substituted 4,5-dihydro-1,3-oxazolyl, 1,2,3-thiadiazolyl, the substituent represented by the formula $-SO_2-NH-R^{12}$ (R^{12} represents hydrogen, 5-methyl-isoxazole, or 2,4-dimethylpyrimidine) or

phenyl optionally substituted by one to three substituents,

wherein

the substituents are each different or identical and selected from the group consisting of hydrogen, halogen, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkanoyl, and carboxy;

R^4 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

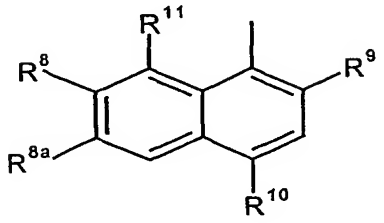
R^5 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

Q represents CH or N;

R^6 represents hydrogen or methyl;

R^7 represents hydrogen or methyl; and

Y represents



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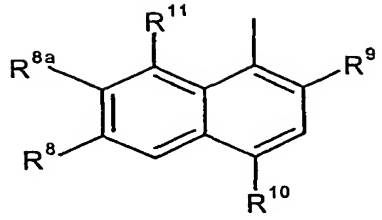
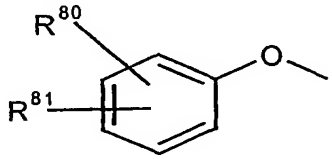


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} C_{3-6} cycloalkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, straight-chain or branched C_{1-6} alkylsulfonamino, or the group represented by the formula



wherein

R^{80} and R^{81} are each identical or different and represent hydrogen, halogen, or straight-chain or branched C_{1-6} alkoxy;

R^{8a} represents hydrogen or halogen;

R^9 represents hydrogen or halogen;

R^{10} represents hydrogen, halogen, or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen, halogen, or nitro.

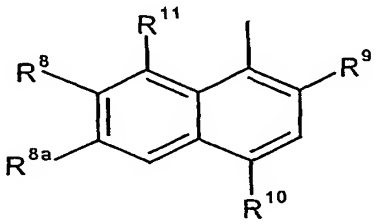
(3) An amine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 or 2,

wherein

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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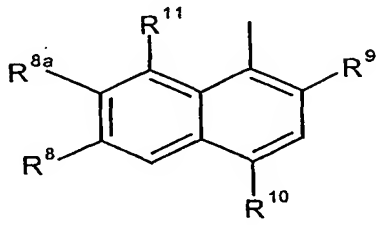


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} C_{3-6} cycloalkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6}

alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, or C_{1-6} alkylsulfonamino;

R^{8a} represents hydrogen, chloro, or fluoro;

R^{9} represents hydrogen or halogen;

R^{10} represents hydrogen, halogen or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen or halogen;

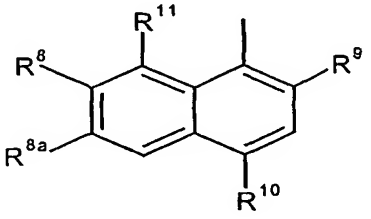
(4) An amine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 or 2,

wherein

R^{6} represents hydrogen;

R^{7} represents hydrogen;

Y represents



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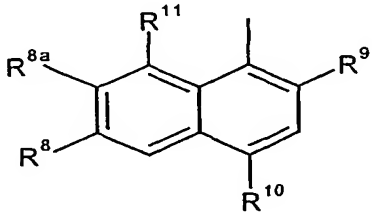


wherein

R^{8} represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} C_{3-6}

cycloalkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, or straight-chain or branched C_{1-6} alkyl-sulfonamino;

R^{8a} represents hydrogen;

R^9 represents hydrogen, bromo, chloro, or fluoro;

R^{10} represents hydrogen,halogen or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen, chloro, or fluoro.

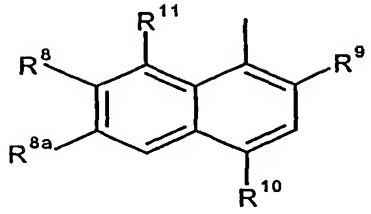
(5) An amine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 or 2,

wherein

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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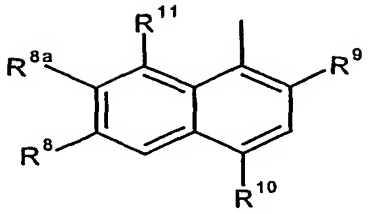


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} cycloalkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, or straight-chain or branched C_{1-6} alkylamino;

R^{8a} represents hydrogen;

R^9 represents bromo or chloro;

R^{10} represents bromo, chloro, or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen.

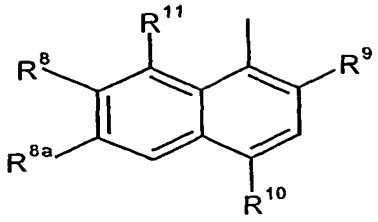
(6) An amine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 or 2,

wherein

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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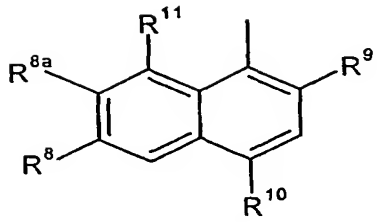


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} cycloalkyl-methoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, or straight-chain or branched C_{1-6} alkylamino;

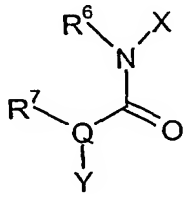
R^{8a} represents hydrogen;

R^9 represents chloro;

R^{10} represents chloro; and

R^{11} represents hydrogen.

(7) An amine derivative of the formula (I)



(I)

wherein

X represents C_{3-8} cycloalkyl optionally fused by benzene, thienyl, thienyl C_{1-6} straight alkyl, quinolyl, 1,2-oxazolyl substituted by R^1, naphthyl optionally substituted by R^4 and R^5, phenyl fused by C_{4-8} cycloalkyl, phenyl fused by saturated C_{4-8} heterocycle having one or two O atoms, carbazolyl of which N-H is substituted by N-R^1, phenyl fused by indanone, phenyl fused by indan, phenyl fused by cyclohexanone, phenyl fused by dihydrofuranone, phenyl substituted by R^1, R^2, and R^3, phenyl C_{1-6} straight alkyl of which phenyl is substituted by R^1, R^2 and R^3, phenyl fused by unsaturated 5-6 membered hetero ring having one or two hetero atoms selected from the group consisting of N, O, S and SO_2, wherein the hetero ring is optionally substituted by R^1,

wherein

R^1, R^2 and R^3 are identical or different and represent hydrogen, halogen, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkylcarbamoyl, carbamoyl, straight-chain or branched C_{1-6} alkoxy, carboxyl, nitro, amino, straight-chain or branched C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, morpholino, straight-chain or branched C_{1-6} alkoxycarbonyl, benzyl, phenoxy, halogen substituted phenoxy, straight-chain or branched C_{1-6} alkylthio, straight-chain or branched C_{1-6} alkanoyl, straight-chain or branched C_{1-6} alkanoylamino, hydroxy substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkoxy, C_{1-6} alkyl substituted 4,5-dihydro-1,3-oxazolyl, 1,2,3-thiadiazolyl, the substituent represented by the formula $-SO_2$-NH-R^{12} (R^{12} represents hydrogen, 5-methyl-isoxazole, or 2,4-dimethylpyrimidine) or

phenyl optionally substituted by one to three substituents,

wherein

the substituents are each identical or different and selected from the group consisting of hydrogen, halogen, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkanoyl, and carboxy;

R^4 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

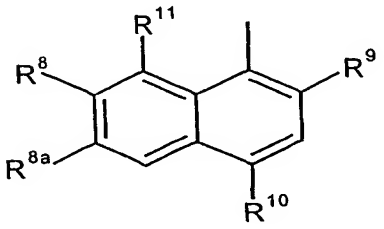
R^5 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

Q represents N;

R^6 represents hydrogen or methyl;

R^7 represents hydrogen or methyl; and

Y represents



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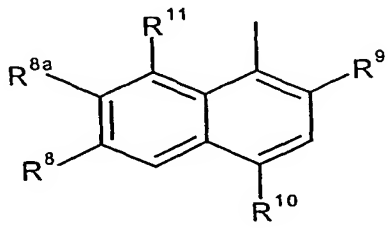
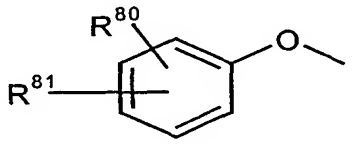


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6} cyclo-alkylmethoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, straight-chain or branched C_{1-6} alkylsulfon-amino, or the group represented by the formula



wherein

R^{80} and R^{81} are each identical or different and represent hydrogen, halogen, or straight-chain or branched C_{1-6} alkoxy;

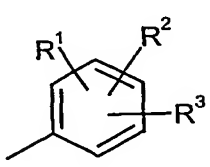
R^{8a} represents hydrogen or halogen;

R^9 and R^{11} are each identical or different and represent hydrogen, halogen, or nitro; and

R^{10} represents hydrogen,halogen, carboxy, carbamoyl, cyano, or straight or branched C_{1-6} alkyl optionally substituted by the substituent, which substituent is selected from the group consisting of hydroxy, amino, di(straight-chain or branched C_{1-6} alkyl)amino, piperidino, morpholino, and methyl-piperazino.

(8) An amine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 7, wherein

X represents



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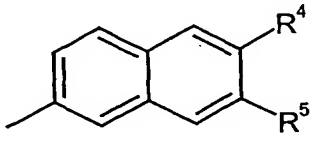

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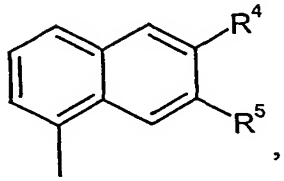

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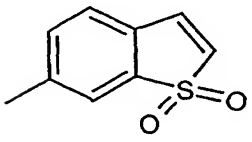

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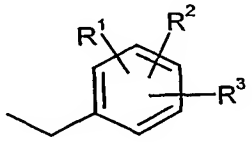

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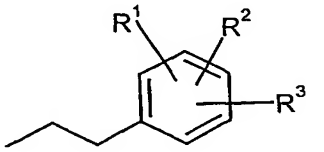

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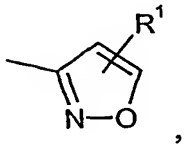

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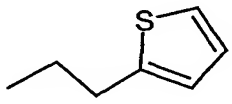

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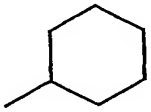
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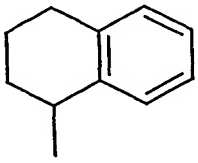
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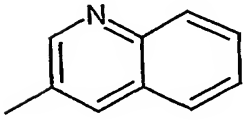

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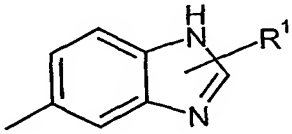

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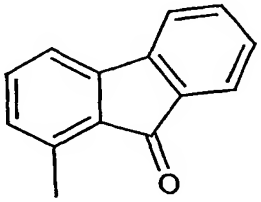

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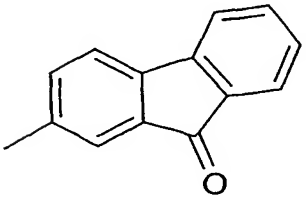

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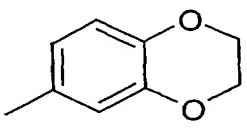

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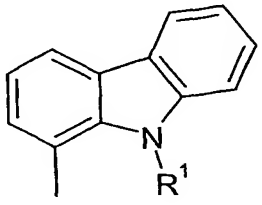

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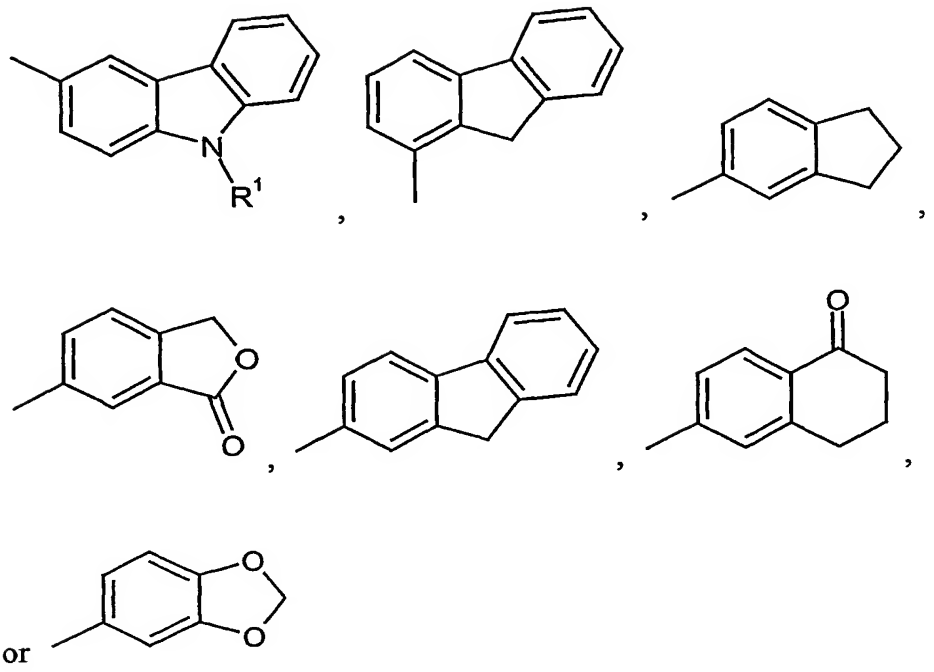


or

wherein

R^1, R^2 and R^3 are identical or different and represent hydrogen, halogen, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkylcarbamoyl, carbamoyl, straight-chain or branched C_{1-6} alkoxy, carboxyl, nitro, amino, straight-chain or branched C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, morpholino, straight-chain or branched C_{1-6} alkoxycarbonyl, benzyl, phenoxy, halogen substituted phenoxy, straight-chain or branched C_{1-6} alkylthio, straight-chain or branched C_{1-6} alkanoyl, straight-chain or branched C_{1-6} alkanoylamino, hydroxy substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkyl, mono-, di- or tri- halogen substituted straight-chain or branched C_{1-6} alkoxy, C_{1-6} alkyl substituted 4,5-dihydro-1,3-oxazolyl, 1,2,3-thiadiazolyl, a substituent

represented by the formula $-SO_2-NH-R^{12}$ (R^{12} represents hydrogen, 5-methyl-isoxazole, or 2,4-dimethylpyrimidine) or

phenyl optionally substituted by one to three substituents,

wherein

the substituents are each identical or different and selected from the group consisting of hydrogen, halogen, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkyl, straight-chain or branched C_{1-6} alkanoyl, and carboxy;

R^4 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

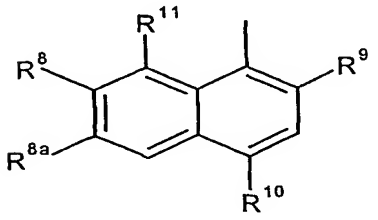
R^5 represents hydrogen, hydroxy, or straight-chain or branched C_{1-6} alkoxy;

Q represents N;

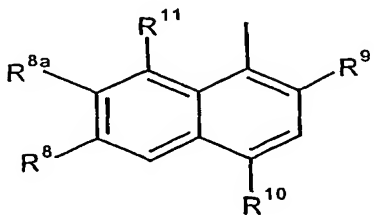
R^6 represents hydrogen or methyl;

R^7 represents hydrogen or methyl; and

Y represents

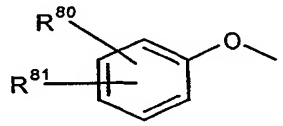


or



wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6}cycloalkyl-methoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyl-oxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)-amino, straight-chain or branched C_{1-6} alkanoylamino, formyl-amino, straight-chain or branched C_{1-6} alkylsulfonamino, or the group represented by the formula



wherein

R^{80} and R^{81} are each identical or different and represent hydrogen, halogen, or straight-chain or branched C_{1-6} alkoxy;

R^{8a} represents hydrogen or halogen;

R^9 represents hydrogen or halogen;

R^{10} represents hydrogen, halogen, or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen, halogen, or nitro.

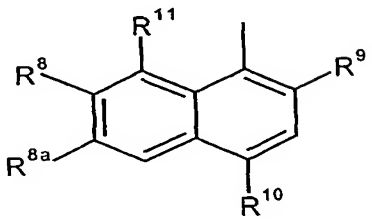
(9) An amine derivative its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 7 or 8,

wherein

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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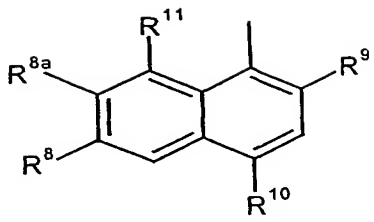


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6}cycloalkyl-methoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, or straight-chain or branched C_{1-6} alkylsulfon-amino;

R^{8a} represents hydrogen, chloro, or fluoro;

R^9 represents hydrogen or halogen;

R^{10} represents hydrogen, halogen or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen or halogen.

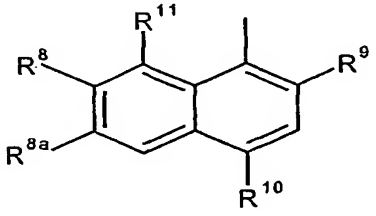
(10) An amine derivative its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 7 or 8,

wherein

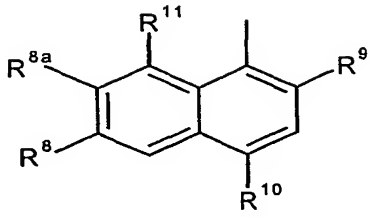
R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



or



wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6}cyclopalkyl-methoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6} alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, formylamino, or straight-chain or branched C_{1-6} alkyl-sulfonamino;

R^{8a} represents hydrogen;

R^9 represents hydrogen, bromo, chloro or fluoro;

R^{10} represents hydrogen, halogen or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen, chloro or fluoro.

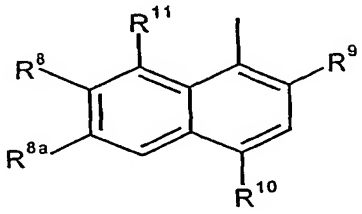
(11) An amine derivative its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 7 or 8,

wherein

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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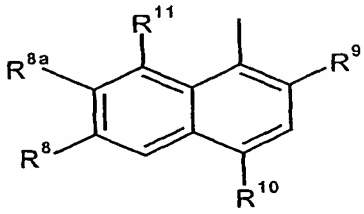


wherein

R^8 represents hydroxy, straight-chain or branched C_{1-6} alkoxy, straight-chain or branched C_{1-6} alkanoyloxy, C_{3-6}cycloalkyl-methoxy, straight-chain or branched C_{2-6} alkenyloxy, benzoyloxy, amino, straight-chain or branched C_{1-6} alkylamino, phenyl C_{1-6} alkylamino, di(straight-chain or branched C_{1-6}

alkyl)amino, straight-chain or branched C_{1-6} alkanoylamino, or straight-chain or branched C_{1-6} alkylsulfonamino;

R^{8a} represents hydrogen;

R^9 represents bromo or chloro;

R^{10} represents bromo, chloro, or straight-chain or branched C_{1-6} alkyl optionally substituted by hydroxy; and

R^{11} represents hydrogen.

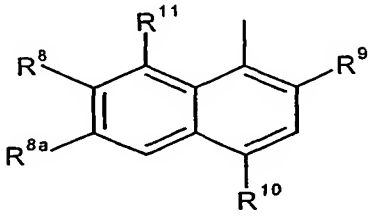
(12) An amine derivative its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 7 or 8,

wherein

R^6 represents hydrogen;

R^7 represents hydrogen;

Y represents



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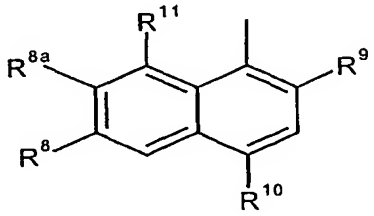


wherein

R^8 represents hydroxy;

R^{8a} represents hydrogen;

R^{9} represents chloro;

R^{10} represents chloro; and

R^{11} represents hydrogen.

(13) The amine derivative as claimed in claim 1 or 2 selected from the group consisting of the following compounds:

N-(7-hydroxy-1-naphthyl)-N'-[4-(trifluoromethyl)phenyl]urea;
N-(7-hydroxy-1-naphthyl)-N'-(4-phenoxyphenyl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7-hydroxy-1-naphthyl)urea;
N-[4-(4-chlorophenoxy)phenyl]-N'-(7-hydroxy-1-naphthyl)urea;
N-(1,1'-biphenyl-3-yl)-N'-(7-hydroxy-1-naphthyl)urea;
N-(7-hydroxy-1-naphthyl)-N'-(3-phenoxyphenyl)urea;
N-(3-chlorophenyl)-N'-(2,4-dibromo-7-hydroxy-1-naphthyl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(2,4-dibromo-7-hydroxy-1-naphthyl)urea;
N-(4-bromobenzyl)-N'-(2-chloro-7-hydroxy-1-naphthyl)urea;
N-(2-chloro-7-hydroxy-1-naphthyl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(2,4-dichloro-7-hydroxy-1-naphthyl)urea;
N-(1,1'-biphenyl-3-yl)-N'-(2-chloro-7-hydroxy-1-naphthyl)urea;
ethyl 3-({[(2,4-dichloro-7-hydroxy-1-naphthyl)amino]carbonyl}amino)benzoate;
N-(2,4-dichloro-7-hydroxy-1-naphthyl)-N'-(2-naphthyl)urea;
N-(2,4-dichloro-7-hydroxy-1-naphthyl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(2'-chloro-1,1'-biphenyl-3-yl)-N'-(2,4-dichloro-7-hydroxy-1-naphthyl)urea;
N-(4-bromo-2-chloro-7-hydroxy-1-naphthyl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea;

N-(2,4-dichloro-7-hydroxy-1-naphthyl)-N'-[4-fluoro-3-(trifluoromethyl)-phenyl]urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7-hydroxy-4-methyl-1-naphthyl)-urea; and
N-(2-chloro-7-hydroxy-4-methyl-1-naphthyl)-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea

or a salt thereof.

(14) A medicament comprising at least one of the compounds, its tautomeric or stereoisomeric form, or a salt thereof as claimed in any one of claim 1 to 13 in combination with at least one pharmaceutically acceptable carrier and/or excipients.

(15) A medicament as claimed in claim 14 for the treatment and/or prophylaxis of urological disorder.

(16) The medicament as claimed in claim 15, wherein said medicament is a VR1 antagonist.

(17) The medicament as claimed in claim 15 for treatment and/or prophylaxis of a disease selected from the group consisting of urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, incontinence and inflammatory disorders.

(18) Use of a compound, its tautomeric or stereoisomeric form, or a salt thereof as claimed in any one of claim 1 to 13 for the preparation of medicament.

(19) Use according to claim 18, for the preparation of medicaments for the treatment of urological disorder.

(20) The process for the preparation of medicaments according to any one of claims 14 to 17, characterized in that the compounds of general formula (I) of claim 1 together with customary auxiliaries in brought into a suitable application form.

(21) Process for controlling urological disorder in humans and animals by administration of a VR1-antagonisticly effective amount of at least one compound according to any of Claims 1 to 3.

FIG. 1

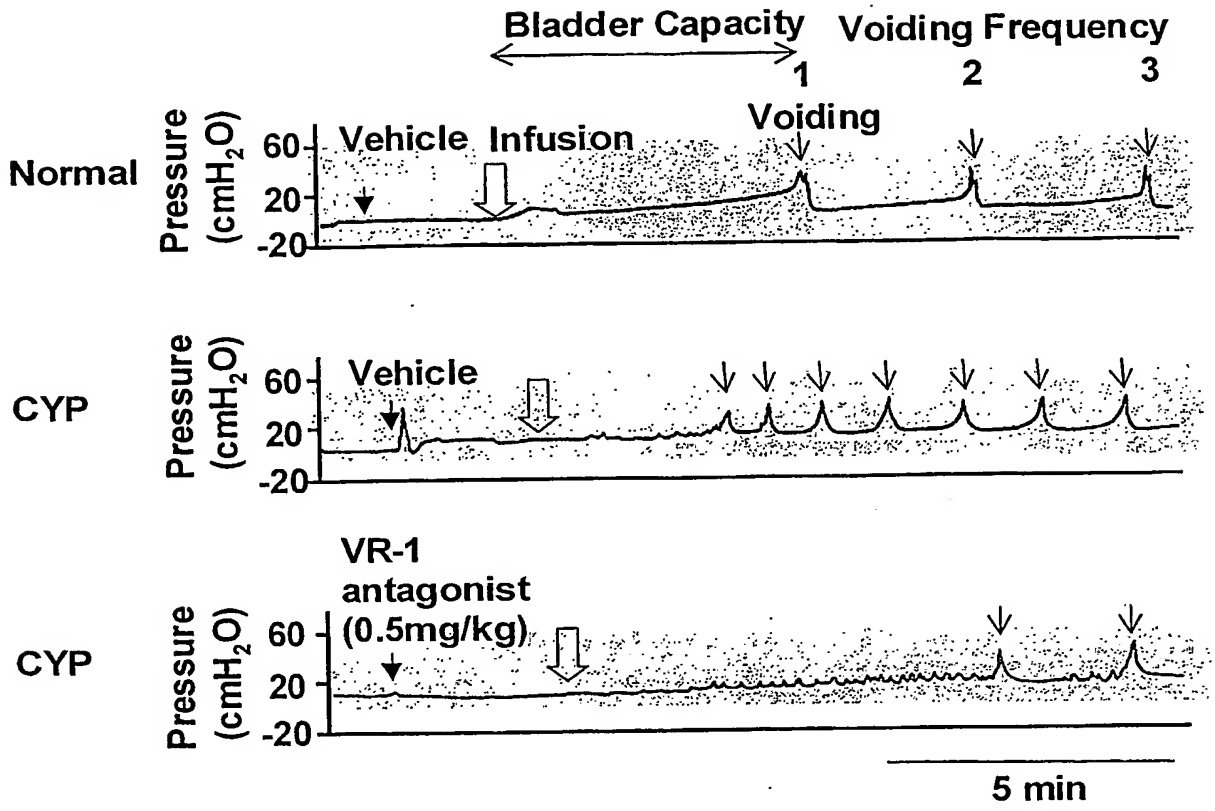


FIG. 2

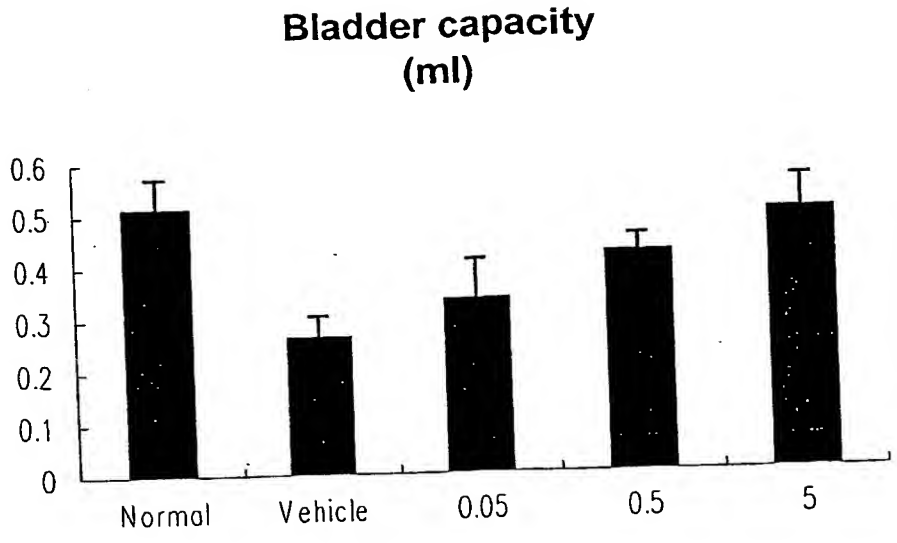
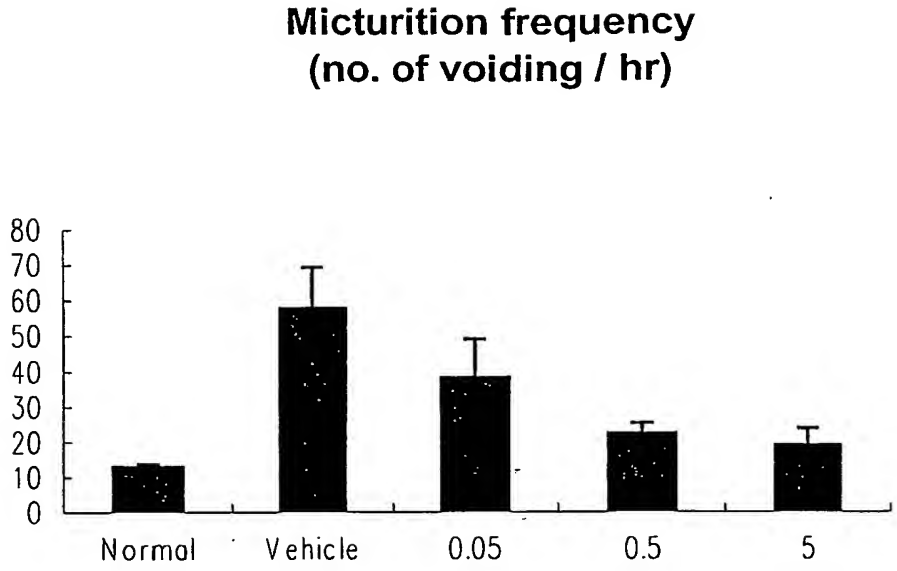


FIG.3



INTERNATIONAL SEARCH REPORT

Inte[illegible]al Application No
[illegible]/EP 02/08493

A. CLASSIFICATION OF SUBJE[illegible]TTER
IPC 7 C07C235/38 C07C275/32 C07C275/34 C07C275/36 C07C275/38
C07C275/40 C07C275/42 C07C311/08 C07C311/47 C07C323/44
C07D209/88 C07D215/38 C07D235/10 C07D239/69 C07D261/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, WPI Data, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HONMA, TERUKI ET AL: "Structure-Based Generation of a New Class of Potent Cdk4 Inhibitors: New de Novo Design Strategy and Library Design" JOURNAL OF MEDICINAL CHEMISTRY (2001), 44(26), 4615-4627 , XP002220243 page 4619; figure 4 ---	1-4,7-10
X	LECLERC, VERONIQUE ET AL: "Synthesis and structure-activity relationships of novel naphthalenic and bioisosteric related amidic derivatives as melatonin receptor ligands" BIOORGANIC & MEDICINAL CHEMISTRY (1998), 6(10), 1875-1887 , XP002220244 page 1880; table 3 ---	1-4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2002	26/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herzog, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/EP 08493

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D261/16 C07D263/10 C07D285/06 C07D295/135 C07D307/88
C07D317/66 C07D319/18 C07D333/20 C07D333/54 A61K31/17
A61P13/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANDRIEUX, J. ET AL: "Synthesis of new naphthalene analogs of serotonin" CHIM. THERAP. (1966), (2), 57-61, XP009000513 page 59; table	1-4
A	WO 00 50387 A (KIM HEE DOO ;OH UHTAEK (KR); PARK YOUNG HO (KR); SUH YOUNG GER (KR) 31 August 2000 (2000-08-31) cited in the application the whole document	1-21

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herzog, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DRAY A: "NEUROPHARMACOLOGICAL MECHANISMS OF CAPSAICIN AND RELATED SUBSTANCES" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 44, no. 4, 18 August 1992 (1992-08-18), pages 611-615, XP000576776 ISSN: 0006-2952 page 611; figure 1 -----	1-21

INTERNATIONAL SEARCH REPORT

ation[redacted]ication No.
PCT/[redacted] 02/08493

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al Application No
T/EP 02/08493

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0050387 A	31-08-2000	AU 2697600 A	14-09-2000
		CN 1342138 T	27-03-2002
		EP 1154989 A1	21-11-2001
		WO 0050387 A1	31-08-2000